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(54) Title: N-BIPHENYLMETHYL AMINOCYCLOALKANECARBOXAMIDE DERIVATIVES

(57) Abstract: N-Biphenyl(substituted methyl) aminocycloalkanecarboxamide derivatives are bradykinin B1 antagonists or inverse agonists useful in the treatment or prevention of symptoms such as pain and inflammation associated with the bradykinin B1 pathway.

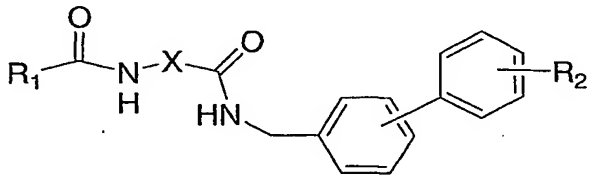
TITLE OF THE INVENTION
N-BIPHENYLMETHYL AMINOCYCLOALKANECARBOXAMIDE DERIVATIVES

BACKGROUND OF THE INVENTION

This invention is directed to aminocycloalkanecarboxamide compounds. In particular, this invention is directed to aminocycloalkanecarboxamide compounds that are bradykinin antagonists or inverse agonists.

Bradykinin ("BK") is a kinin which plays an important role in the pathophysiological processes accompanying acute and chronic pain and inflammation. Bradykinin (BK), like other kinins, is an autacoid peptide produced by the catalytic action of kallikrein enzymes on plasma and tissue precursors termed kininogens. The biological actions of BK are mediated by at least two major G-protein-coupled BK receptors termed B1 and B2. It is generally believed that B2 receptors, but not B1 receptors, are expressed in normal tissues and that inflammation, tissue damage or bacterial infection can rapidly induce B1 receptor expression. This makes the B1 receptor a particularly attractive drug target. The putative role of kinins, and specifically BK, in the management of pain and inflammation has provided the impetus for developing potent and selective BK antagonists. In recent years, this effort has been heightened with the expectation that useful therapeutic agents with analgesic and anti-inflammatory properties would provide relief from maladies mediated through a BK receptor pathway (see e.g., M.G. Bock and J. Longmore, *Current Opinion in Chem. Biol.*, 4:401-406(2000)). Accordingly, there is a need for novel compounds that are effective in blocking or reversing activation of bradykinin receptors. Such compounds would be useful in the management of pain and inflammation, as well as in the treatment or prevention of diseases and disorders mediated by bradykinin; further, such compounds are also useful as research tools (*in vivo* and *in vitro*).

Canadian Published Application No. 2,050,769 discloses compounds of the formula:



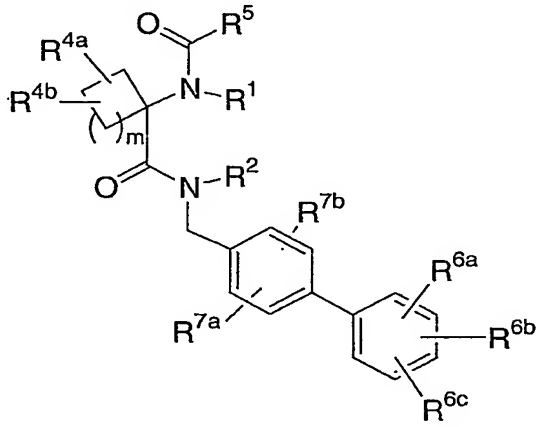
which are intermediates in the preparation of angiotensin II antagonists.

SUMMARY OF THE INVENTION

The present invention provides biphenyl cycloalkanecarboxamide derivatives which are bradykinin antagonists or inverse agonists, pharmaceutical compositions containing such compounds, and methods of using them as therapeutic agents.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds of formula I and pharmaceutically acceptable salts thereof:



I

wherein

R^1 and R^2 are independently selected from

(1) hydrogen and

(2) C_{1-4} alkyl;

R^{4a} and R^{4b} are independently selected form

(1) hydrogen,

(2) halogen, and

(3) C_{1-4} alkyl optionally substituted with 1 to 4 groups selected from halogen, OR^a, $OC(O)R^a$, $S(O)_kR^d$, $OS(O)_2R^d$, and NR^1R^2, or

R^{4a} and R^{4b} together with the carbon atom to which they are both attached form an exo-cyclic methylene optionally substituted with 1 to 2 groups selected from C_{1-4} alkyl optionally substituted with 1-5 halogens and C_{1-4} alkyloxy;

R^5 is selected from

(1) C_{1-6} alkyl optionally substituted with 1 to 5 groups independently selected from halogen, nitro, cyano, OR^a, SR^a, COR^a, SO_2R^d, CO_2R^a, $OC(O)R^a$, NR^bR^c, $NR^bC(O)R^a$, $NR^bC(O)_2R^a$, $C(O)NR^bR^c$, C_{3-8} cycloalkyl,

(2) C_{3-8} cycloalkyl optionally substituted with 1 to 5 groups independently selected from halogen, nitro, cyano and phenyl,

(3) C_{3-6} alkynyl,

(4) C_{2-6} alkenyl optionally substituted with hydroxyethyl,

(5) $(CH_2)_k$-aryl optionally substituted with 1 to 3 groups independently selected from halogen, nitro, cyano, OR^a, SR^a, $C(O)_2R^a$, C_{1-4} alkyl and C_{1-3} haloalkyl, wherein aryl is selected from phenyl, 3,4-methylenedioxyphenyl and naphthyl;

(6) $(CH_2)_k$-heterocycle optionally substituted with 1 to 3 groups independently selected from halogen, nitro, cyano, OR^a, SR^a, C_{1-4} alkyl and C_{1-3} haloalkyl wherein said heterocycle is selected from (a) a 5-membered heteroaromatic ring having a ring heteroatom selected from N, O and S, and optionally having up to 3 additional ring nitrogen atoms wherein said ring is optionally benzo-fused; (b) a 6-membered heteroaromatic ring containing from 1 to 3 ring nitrogen atoms and N-oxides thereof, wherein said ring is optionally benzo-fused; and (c) a 5- or 6-membered non-aromatic heterocyclic ring selected from tetrahydrofuranyl, 5-oxo-tetrahydrofuranyl, 2-oxo-2H-pyranyl, 6-oxo-1,6-dihydropyridazinyl,

(7) $C(O)_2R^a$, and

(8) $C(O)NR^bR^c$;

R^{6a} is selected from

(1) C_{1-8} alkyl optionally substituted with 1-5 groups independently selected from halogen, nitro, cyano, COR^a, CO_2R^a, $C(O)NR^bR^c$, OR^a, $OC(O)R^a$, SR^a, SO_2R^d, $S(O)R^d$, NR^bR^c, $NR^bC(O)R^a$, $NR^bSO_2R^d$, $NR^bCO_2R^a$,

(2) C_{3-8} cycloalkyl,

(3) C_{2-8} alkenyl optionally substituted with CO_2R^a,

(4) halogen,

(5) cyano,

(6) nitro,

(7) NR^bR^c,

(8) $NR^bC(O)R^a$,
(9) $NR^bCO_2R^a$,
(10) $NR^bC(O)NR^bR^c$,
(11) $NR^bC(O)NR^bCO_2R^a$,
(12) $NR^bSO_2R^d$,
(13) CO_2R^a,
(14) COR^a,
(15) $C(O)NR^bR^c$,
(16) $C(O)NHOR^a$,
(17) $C(=NOR^a)R^a$,
(18) $C(=NOR^a)NR^bR^c$,
(19) OR^a,
(20) $OC(O)R^a$,
(21) $S(O)_kR^d$,
(22) $SO_2NR^bR^c$, and
(23) optionally substituted heterocycle where the heterocycle is a 5-membered heteroaromatic ring having a ring heteroatom selected from N, O and S, and optionally having up to 3 additional ring nitrogen atoms, 4,5-dihydro-oxazolyl and 4,5-dihydro-1,2,4-oxadiazolyl, and wherein said substituent is 1 to 3 groups independently selected from C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms, OR^a or $OC(O)R^a$,

R^{6b} and R^{6c} are independently selected from

(1) hydrogen, and
(2) a group from R^{6a}; with the proviso that not more than one of R^{6a}, R^{6b}, and R^{6c} is a heterocycle;

R^{7a} and R^{7b} are independently selected from

(1) hydrogen,
(2) halogen,
(3) cyano,
(4) nitro,
(5) OR^a,
(6) CO_2R^a,
(7) $C(O)NR^bR^c$,
(8) C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms,

(9) NR^bR^c, and

(10) $S(O)_kR^d$;

R^a is selected from

(1) hydrogen,

(2) C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms,

(3) phenyl optionally substituted with 1 to 3 groups independently selected from halogen, cyano, nitro, OH, C_{1-4} alkyloxy, C_{3-6} cycloalkyl and C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms,

(4) C_{3-6} cycloalkyl, and

(5) pyridyl optionally substituted with 1 to 3 groups independently selected from halogen and C_{1-4} alkyl;

R^b and R^c are independently selected from

(1) hydrogen,

(2) C_{1-4} alkyl optionally substituted with 1 to 5 groups independently selected from halogen , amino, mono-C_{1-4}alkylamino, di-C_{1-4}alkylamino, and SO_2R^d,

(3) $(CH_2)_k$-phenyl optionally substituted with 1 to 3 groups selected from halogen, cyano, nitro, OH, C_{1-4} alkyloxy, C_{3-6} cycloalkyl and C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms, and

(4) C_{3-6} cycloalkyl, or

R^b and R^c together with the nitrogen atom to which they are attached form a 4-, 5-, or 6-membered ring optionally containing an additional heteroatom selected from N, O, and S; or

R^b and R^c together with the nitrogen atom to which they are attached form a cyclic imide;

R^d is selected from

(1) C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms,

(2) C_{1-4} alkyloxy, and

(3) phenyl optionally substituted with 1 to 3 groups selected from halogen, cyano, nitro, OH, C_{1-4} alkyloxy, C_{3-6} cycloalkyl and C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms;

k is 0, 1 or 2; and

m is 0 or 1.

For compounds of formula I, examples of R^1 and R^2 include hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl and sec-butyl. In one embodiment of formula I are compounds wherein R^1 and R^2 are each hydrogen.

Examples R^{4a} and R^{4b} for compounds of formula I include hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, t-butyl, chlorine, fluorine, bromine, chloromethyl, 1-chloroethyl, hydroxymethyl, 2-methoxyethyl, ethoxymethyl, acetyloxymethyl, methylthiomethyl, aminomethyl, methylamino-methyl, (dimethylamino)methyl, (methylsulfonyl)oxymethyl, and the like; or R^{4a} and R^{4b} on the same carbon atom taken together represent methylene. In one embodiment of formula I are compounds wherein one of R^{4a} and R^{4b} is hydrogen and the other is selected from hydrogen, halogen and C_{1-4} alkyl optionally substituted with a group selected from halogen, OR^a, $OC(O)R^a$, $S(O)_kR^d$, $OS(O)_2R^d$, and NR^1R^2, or R^{4a} and R^{4b} together with the carbon atom to which they are both attached form an exo-cyclic methylene. In one subset thereof R^{4a} and R^{4b} are each hydrogen; in another subset R^{4a} is hydrogen and R^{4b} is selected from CH_2-halogen, CH_2-OR^a, CH_2-$OC(O)R^a$, CH_2-$S(O)_kR^d$, CH_2-$OS(O)_2R^d$, and CH_2-NR^1R^2; in a further subset R^{4a} is hydrogen and R^{4b} is selected from hydroxymethyl, acetyloxymethyl, chloromethyl, (methanesulfonyl)oxymethyl, (methylthio)methyl and (dimethylamino)methyl.

Examples of R^5 for compounds of formula I include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, t-butyl, 1-ethylpropyl, 2,2-dimethyl-propyl, bromomethyl, chloromethyl, dichloromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl, cyanomethyl, aminomethyl, acetylaminomethyl, dimethyl-aminomethyl, hydroxymethyl, methoxymethyl, ethoxymethyl, methylsulfonylmethyl, phenylthiomethyl, phenoxymethyl, 1-aminoethyl, 1-acetylaminomethyl, 1-imidazolyl-methyl, t-butoxycarbonylaminomethyl, 3-pyridylcarbonylmethyl, 1-chloroethyl, 1,1-dichloroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 2-methoxyethyl, 2-phenylethyl, 2-cyclopentylethyl, 2-carboxyethyl, 2-methoxy-2-oxoethyl, 2-nitroethyl, 1,1-difluoro-1-hydroxypropyl, 1-hydroxypropyl, 2-oxopropyl, 3-methoxy-3-oxopropyl, 1-cyano-cyclopropyl, cyclopropyl, cyclopentyl, 2-phenylcyclopropyl, allyl, ethenyl, 1-(1-hydroxyethyl)vinyl, 3-butynyl, propargyl, phenyl, benzyl, 3,5-bis(trifluoromethyl)-phenyl, 2,4-difluorophenyl, 4-methylphenyl, 3,4-dimethoxybenzyl, 3,4-dimethoxy-phenyl, 4-cyanophenyl, 3-nitrophenyl, 2-naphthyl, 3,4-methylenedioxyphenyl, 3-

cyanophenyl, 2-cyanophenyl, 3-fluorophenyl, 3-methoxyphenyl, 3-chlorophenyl, 3,4-dichlorophenyl, 3,5-dimethoxyphenyl, 3-trifluoromethylphenyl, 3-methylphenyl, 3,5-dichlorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 3-nitro-5-(trifluoromethyl)-phenyl, 5-isoxazolyl, 2-benzothienyl, 2-thienylmethyl, 3-pyridyl, 4-pyridyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 5-methyl-3-isoxazolyl, 3-tetrahydrofuranyl, 4-methyl-1,2,5-oxadiazol-3-yl, 5-carboxy-3-pyridyl, 6-hydroxy-2-pyridyl, 5-hydroxy-3-pyridyl, 2-hydroxy-3-pyridyl, 2-methyoxy-3-pyridyl, 6-chloro-2-pyridyl, 2-chloro-3-pyridyl, 5-chloro-3-pyridyl, 5-fluoro-3-pyridyl, 5-bromo-3-pyridyl, 5-methyl-3-pyridyl, 3-(trifluoromethyl)-4-pyridyl, 5-(trifluoromethyl)-3-pyridyil, 1-methyl-4-pyrazolyl, 1-pyrazolylmethyl, 1-methyl-2-imidazolyl, 1,2,4-triazol-1-ylmethyl, 4-thiazolyl, 5-oxo-tetrahydrofuran-2-yl, 2-oxo-5-pyranyl, 3-isoxazolyl, 3-pyridazinyl, 5-pyrimidinyl, 4-pyrimidinyl, 1-methyl-5-pyrazolyl, 1-methyl-3-pyrazolyl, 5-thiazolyl, 5-methyl-1-pyrazolylmethyl, (3-methyl-1,2,4-triazol-5-yl)methyl, 2-(1,2,4-triazol-1-yl)ethyl, 5-methyl-4-thiazolyl, 2-quinoxalinyl, methoxycarbonyl, aminocarbonyl, methylamino-carbonyl, dimethylaminocarbonyl, 2-(dimethylamino)ethylaminocarbonyl, benzyl-aminocarbonyl, 2-phenethylaminocarbonyl.

In one embodiment of formula I are compounds wherein R^5 is C_{1-6} alkyl optionally substituted with 1 to 5 groups independently selected from halogen, nitro, cyano, OR^a, SR^a, COR^a, SO_2R^d, CO_2R^a, $OC(O)R^a$, NR^bR^c, $NR^bC(O)R^a$, $NR^bCO_2R^a$, $C(O)NR^bR^c$, and C_{3-8} cycloalkyl. In a one subset thereof are compounds wherein R^5 is selected from C_{1-5} alkyl and C_{1-3} alkyl substituted with 1 to 5 groups selected from halogen, nitro, cyano, hydroxy, C_{1-4} alkoxy, phenoxy, phenylthio, C_{1-4} alkoxycarbonyl, C_{1-4} alkylsulfonyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} alkylcarbonylamino, C_{1-4} alkoxycarbonylamino, and C_{1-4} alkanoyl. In a further subset R^5 is selected from C_{1-3} alkyl substituted with 1 to 5 halogen atoms where said halogen is fluoro or chloro.

In another embodiment of formula I are compounds wherein R^5 is C_{3-6} cycloalkyl optionally substituted with 1 to 3 groups independently selected from halogen, nitro, cyano and phenyl. In one subset R^5 is C_{3-6} cycloalkyl optionally substituted with a group selected from cyano and phenyl.

In another embodiment of formula I are compounds wherein R^5 is $(CH_2)_k$-aryl optionally substituted with 1 to 3 groups independently selected from halogen, nitro, cyano, OR^a, SR^a, C_{1-4} alkyl and C_{1-3} haloalkyl, wherein aryl is selected from phenyl, 3,4-methylenedioxyphenyl and naphthyl. In one subset thereof, R^5 is $(CH_2)_k$-phenyl optionally substituted with 1 to 3 groups independently selected

from halogen, trifluoromethyl, nitro, cyano, C_{1-4} alkoxy and C_{1-4} alkyl; in a further subset R^5 is phenyl optionally substituted with 1 to 2 groups selected from methyl, trifluoromethyl, halogen, cyano, nitro and methoxy.

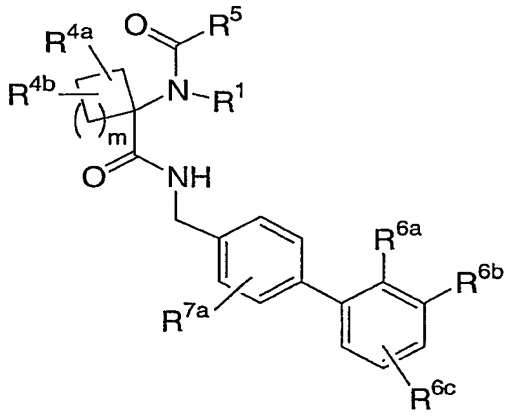
In another embodiment of formula I are compounds wherein R^5 is $(CH_2)_k$-heterocycle optionally substituted with 1 to 2 groups independently selected from halogen, nitro, cyano, OR^a, SR^a, C_{1-4} alkyl and C_{1-3} haloalkyl wherein said heterocycle is selected from isoxazolyl, thienyl, pyridinyl, benzothienyl, furyl, tetrahydrofuranyl, oxadiazolyl, 1-oxidopyridinyl, pyrazolyl, imidazolyl, 1,2,4-triazolyl, thiazolyl, 5-oxotetrahydrofuranyl, 2-oxo-2H-pyranyl, 6-oxo-1,6-dihydro-pyridazinyl, oxazolyl, pyridazinyl, pyrimidinyl and quinoxalinyl. In one subset thereof R^5 is selected from isoxazolyl optionally substituted with 1 or 2 C_{1-4} alkyl, thienyl, pyridinyl optionally substituted with hydroxy, trifluoromethyl or halogen, benzothienyl, furyl, tetrahydrofuranyl, oxadiazolyl optionally substituted with C_{1-4} alkyl, 1-oxidopyridinyl optionally substituted with halogen or C_{1-4} alkyl, pyrazolyl optionally substituted with C_{1-4} alkyl, imidazolyl optionally substituted with C_{1-4} alkyl, 1,2,4-triazolyl optionally substituted with C_{1-4} alkyl, thiazolyl optionally substituted with C_{1-4} alkyl, 5-oxotetrahydrofuranyl, 2-oxo-2H-pyranyl, 6-oxo-1,6-dihydropyridazinyl, oxazolyl, pyridazinyl, pyrimidinyl and quinoxalinyl. In another subset R^5 is selected from 5-isoxazolyl and 5-pyrimidinyl.

For compounds of formula I examples of R^{6a} include 1-methylethyl, 1-hydroxyethyl, methoxymethyl, 2-oxo-2-methoxyethyl, carboxy, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, phenoxycarbonyl, cyclopentoxycarbonyl, cyclobutoxycarbonyl, cyclopropoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, 4-trifluoromethylphenoxycarbonyl, methoxyaminocarbonyl, methoxycarbonylmethyl, formyl, hydroxy, 3-methyl-1,2,4-oxadiazol-5-yl, 5-methyl-1,2,4-oxadiazol-3-yl, 1-methyl-5-tetrazolyl, 2-methyl-5-tetrazolyl, cyano, hydroxy, methoxy, difluoromethoxy, trifluoromethoxy, trifluoromethyl, chloro, fluoro, methylaminosulfonyl, dimethylaminosulfonyl, methoxycarbonylamino, ethoxycarbonylamino, 2-fluoroethoxycarbonylamino, isopropoxycarbonylamino, methylaminocarbonylamino, dimethylamino, methylaminocarbonyl, isopropylaminocarbonyl, ethylaminocarbonyl, cyclopropylaminocarbonyl, cyclobutylaminocarbonyl, dimethylaminocarbonyl and aminocarbonyl; examples for R^{6b} for compounds of formula I include hydrogen, chloro, fluoro, methyl and methoxycarbonyl; example of R^{6c} include hydrogen, chloro,

fluoro and methyl; and examples of R^{7a} and R^{7b} include hydrogen, hydroxy, methoxy, methylamino, methylsulfonyl, chloro and fluoro.

In another embodiment of formula I are compounds wherein m is 0.

In another embodiment of formula I are compounds represented by formula I(1):



I(1)

wherein m, R^1, R^{4a}, R^{4b}, R^5, R^{6a}, R^{6b}, R^{6c} and R^{7a} have the same definitions as provided under formula I.

In a subset of formula I(1) are compounds wherein R^{6a} is selected from (1) CO_2R^a, (2) $C(O)NHOR^a$, (3) cyano, (4) halogen, (5) OR^a, (6) C_{1-8} alkyl optionally substituted with 1-5 halogen atoms, or a group selected from CO_2R^a, $C(O)NR^bR^c$ and OR^a, (7) $C(O)NR^bR^c$, (8) $NR^bC(O)NR^bR^c$, (9) $NR^bC(O)OR^a$, and (10) optionally substituted heterocycle where the heterocycle is selected from oxadiazolyl and tetrazolyl and wherein said substituent is 1 to 3 groups independently selected from C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms, OR^a or $OC(O)R^a$. In a further subset are compounds wherein R^{6a} is selected from CO_2R^a, $C(O)NHOR^a$, methyltetrazolyl, methyloxadiazolyl, $NR^bC(O)NR^bR^c$, and $NR^bC(O)OR^a$.

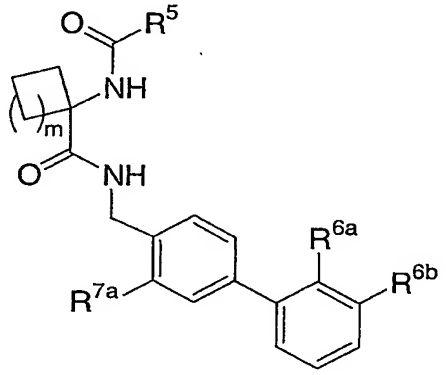
In another subset of formula I(1) are compounds wherein R^{6b} is selected from hydrogen, halogen and CO_2R^a. In a further subset R^{6b} is hydrogen or halogen.

In another subset of formula I(1) are compounds where R^{6a} is selected from (1) CO_2R^a, (2) $C(O)NHOR^a$, (3) cyano, (4) halogen, (5) OR^a, (6) C_{1-8} alkyl optionally substituted with 1-5 halogen atoms, or a group selected from CO_2R^a,

$C(O)NR^bR^c$ and OR^a, (7) $C(O)NR^bR^c$, (8) $NR^bC(O)NR^bR^c$, (9) $NR^bC(O)OR^a$, and (10) optionally substituted heterocycle where the heterocycle is selected from oxadiazolyl and tetrazolyl and wherein said substituent is 1 to 3 groups independently selected from C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms, OR^a or $OC(O)R^a$; R^{6b} is selected from hydrogen and halogen; and R^{6c} is hydrogen.

In another subset of formula I(1) are compounds wherein R^5 is selected from C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms or a cyano group, C_{3-6} cycloalkyl, isoxazolyl, pyrimidinyl and pyridinyl (and N-oxide thereof) optionally substituted with halogen.

In another embodiment of formula I are compounds represented by formula I(2):



I(2)

wherein m, R^5, R^{6a}, R^{6b} and R^{7a} have the same definitions as provided under formula I.

In another embodiment of formula I(2), R^{6b} is hydrogen or halogen. In one subset R^{6b} is hydrogen; in another subset R^{6b} is fluorine or chlorine.

In another embodiment of formula I(2), R^{6a} is selected from (1) CO_2R^a, (2) $C(O)NHOR^a$, (3) cyano, (4) halogen, (5) OR^a, (6) C_{1-8} alkyl optionally substituted with 1-5 halogen atoms, or a group selected from CO_2R^a, $C(O)NR^bR^c$ and OR^a, (7) $C(O)NR^bR^c$, (8) $NR^bC(O)NR^bR^c$, (9) $NR^bC(O)OR^a$, and (10) optionally substituted heterocycle where the heterocycle is selected from oxadiazolyl and tetrazolyl and wherein said substituent is 1 to 3 groups independently selected from C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms, OR^a or $OC(O)R^a$. In one subset R^{6a} is selected from CO_2R^a, $C(O)NHOR^a$, methyltetrazolyl,

methyloxadiazolyl, $NR^bC(O)NR^bR^c$, and $NR^bC(O)OR^a$. In a further subset R^{6a} is selected from CO_2R^a, methyltetrazolyl and methyloxadiazolyl,

In another embodiment R^{7a} is hydrogen or halogen. In one subset R^{7a} is hydrogen. In another subset R^{7a} is fluorine. In yet another subset R^{6b} is hydrogen, fluorine or chlorine, and R^{7a} is hydrogen or fluorine.

In another embodiment of formula I(2) R^5 is selected from C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms or a cyano group, C_{3-6} cycloalkyl, isoxazolyl, pyrimidinyl and pyridinyl (and N-oxide thereof) optionally substituted with halogen.

In another embodiment of formula I(2) are compounds wherein m is 0 or 1, R^{6a} is 2-methyl-2H-tetrazol-5-yl, 3-methyl-1,2,4-oxadiazol-5-yl, CO_2R^a or $C(O)NHOR^a$ wherein R^a is C_{1-4} alkyl, particularly methyl; R^{6b} is hydrogen, fluorine or chlorine; R^5 is selected from C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms or a cyano group, C_{3-6} cycloalkyl, isoxazolyl, pyrimidinyl and pyridinyl (and N-oxide thereof) optionally substituted with halogen or trifluoromethyl, particularly trifluoromethyl, difluoromethyl, chlorodifluromethyl, 2,2,2-trifluoroethyl, pentafluoromethyl, cyanomethyl, 5-pyrimidinyl, 5-isoxazolyl and 5-bromo-3-pyridinyl and N-oxide thereof; and R^{7a} is hydrogen or fluorine.

Unless otherwise stated, the following terms have the meanings indicated below:

"Alkyl" as well as other groups having the prefix "alk" such as, for example, alkoxy, alkanoyl, alkenyl, alkynyl and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl and the like.

"Alkenyl" means a linear or branched carbon chain containing at least one C=C bond. Examples of alkenyl include allyl, 2-butenyl, 3-butenyl, 1-methyl-2-propenyl, and the like.

"Alkynyl" means a linear or branched carbon chain containing at least one C≡C bond. Examples of alkynyl include propargyl, 2-butynyl, 3-butynyl, 1-methyl-2-propynyl, and the like.

"Cyclic imide" includes succinimide, maleimide, phthalimide and the like.

"Cycloalkyl" means carbocycles containing no heteroatoms, and

includes mono-, bi- and tricyclic saturated carbocycles, as well as fused ring systems. Such fused ring systems can include one ring that is partially or fully unsaturated such as a benzene ring to form fused ring systems such as benzofused carbocycles. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydro-naphthalene, adamantane, indanyl, indenyl, fluorenyl, 1,2,3,4-tetrahydronaphthalene and the like.

"Haloalkyl" means an alkyl radical as defined above wherein at least one and up to all of the hydrogen atoms are replaced with a halogen. Examples of such haloalkyl radicals include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl and the like.

"Halogen" means fluorine, chlorine, bromine and iodine.

"Optionally substituted" is intended to include both substituted and unsubstituted. Thus, for example, optionally substituted aryl could represent a pentafluorophenyl or a phenyl ring.

Optical Isomers - Diastereomers - Geometric Isomers - Tautomers

Compounds described herein may contain an asymmetric center and may thus exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centers, they may additionally exist as diastereomers. The present invention includes all such possible stereoisomers as substantially pure resolved enantiomers, racemic mixtures thereof, as well as mixtures of diastereomers. The above Formula I is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of Formula I and pharmaceutically acceptable salts thereof. Diastereoisomeric pairs of enantiomers may be separated by, for example, fractional crystallization from a suitable solvent, and the pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid or base as a resolving agent or on a chiral HPLC column. Further, any enantiomer or diastereomer of a compound of the general Formula I may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist with different points of attachment of hydrogen, referred to as tautomers. Such an example may be a ketone and its enol form known as keto-enol tautomers. The individual tautomers as well as mixture thereof are encompassed with compounds of Formula I.

Salts

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts prepared from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines derived from both naturally occurring and synthetic sources. Pharmaceutically acceptable organic non-toxic bases from which salts can be formed include, for example, arginine, betaine, caffeine, choline, N,N'-dibenzyl-ethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, dicyclohexylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric,

tartaric, p-toluenesulfonic acid and the like. Preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

Prodrugs

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds of this invention which are readily convertible in vivo into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various conditions described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs," ed. H. Bundgaard, Elsevier, 1985. Metabolites of these compounds include active species produced upon introduction of compounds of this invention into the biological milieu.

Pharmaceutical Compositions

Another aspect of the present invention provides pharmaceutical compositions which comprises a compound of Formula I and a pharmaceutically acceptable carrier. The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) (pharmaceutically acceptable excipients) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of Formula I, additional active ingredient(s), and pharmaceutically acceptable excipients.

The pharmaceutical compositions of the present invention comprise a compound represented by Formula I (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and

intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

In practice, the compounds represented by Formula I, or pharmaceutically acceptable salts thereof, of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound represented by Formula I, or pharmaceutically acceptable salts thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of Formula I. The compounds of Formula I, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.1mg to about 500mg of the active ingredient and each cachet or capsule preferably containing from about 0.1mg to about 500mg of the active ingredient.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion

medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound represented by Formula I of this invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in moulds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound described by Formula I, or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

The following are examples of representative pharmaceutical dosage forms for the compounds of Formula I:

Injectable Suspension (I.M.)	mg/mL
Compound of Formula I	10
Methylcellulose	5.0
Tween 80	0.5
Benzyl alcohol	9.0
Benzalkonium chloride	1.0

Water for injection to a total volume of 1 mL

Tablet	mg/tablet
Compound of Formula I	25
Microcrystalline Cellulose	415
Povidone	14.0
Pregelatinized Starch	43.5
Magnesium Stearate	2.5
	500

Capsule	mg/capsule
Compound of Formula I	25
Lactose Powder	573.5
Magnesium Stearate	1.5
	600

Utilities

Compounds of this invention are antagonists or inverse agonists of bradykinin receptor, in particular the bradykinin B1 receptor, and as such are useful in the treatment and prevention of diseases and conditions mediated through the bradykinin receptor pathway such as pain and inflammation. The compounds would be effective in the treatment or prevention of pain including, for example, visceral pain (such as pancreatitis, interstitial cystitis, renal colic), neuropathic pain (such as postherpetic neuralgia, nerve injury, the "dynias", e.g., vulvodynia, phantom limb pain, root avulsions, painful traumatic mononeuropathy, painful polyneuropathy), central pain syndromes (potentially caused by virtually any lesion at any level of the nervous system), and postsurgical pain syndromes (eg, postmastectomy syndrome, postthoracotomy syndrome, stump pain)), bone and joint pain (osteoarthritis), repetitive motion pain, dental pain, cancer pain, myofascial pain (muscular injury, fibromyalgia), perioperative pain (general surgery, gynecological), chronic pain, dysmennorhea, as well as pain associated with angina, and inflammatory pain of varied origins (e.g. osteoarthritis, rheumatoid arthritis, rheumatic disease, teno-synovitis and gout).

Further, the compounds of this invention can also be used to treat hyperreactive airways and to treat inflammatory events associated with airways

disease e.g. asthma including allergic asthma (atopic or non-atopic) as well as exercise-induced bronchoconstriction, occupational asthma, viral- or bacterial exacerbation of asthma, other non-allergic asthmas and "wheezy-infant syndrome". Compounds of the present invention may also be used to treat chronic obstructive pulmonary disease including emphysema, adult respiratory distress syndrome, bronchitis, pneumonia, allergic rhinitis (seasonal and perennial), and vasomotor rhinitis. They may also be effective against pneumoconiosis, including aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

Compounds of the present invention may also be used for the treatment of inflammatory bowel disease including Crohn's disease and ulcerative colitis, irritable bowel syndrome, pancreatitis, nephritis, cystitis (interstitial cystitis), uveitis, inflammatory skin disorders such as psoriasis and eczema, rheumatoid arthritis and edema resulting from trauma associated with burns, sprains or fracture, cerebral edema and angioedema. They may be used to treat diabetic vasculopathy, diabetic neuropathy, diabetic retinopathy, post capillary resistance or diabetic symptoms associated with insulitis (e.g. hyperglycemia, diuresis, proteinuria and increased nitrite and kallikrein urinary excretion). They may be used as smooth muscle relaxants for the treatment of spasm of the gastrointestinal tract or uterus. Additionally, they may be effective against liver disease, multiple sclerosis, cardiovascular disease, e.g. atherosclerosis, congestive heart failure, myocardial infarct; neurodegenerative diseases, eg. Parkinson's and Alzheimers disease, epilepsy, septic shock e.g. as anti-hypovolemic and/or anti-hypotensive agents, headache including cluster headache, migraine including prophylactic and acute use, closed head trauma, cancer, sepsis, gingivitis, osteoporosis, benign prostatic hyperplasia and hyperactive bladder. Animal models of these diseases and conditions are generally well known in the art, and may be suitable for evaluating compounds of the present invention for their potential utilities. Finally, compounds of the present invention are also useful as research tools (*in vivo* and *in vitro*).

The compounds of this invention are useful in the treatment of pain and inflammation by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

The compounds would be effective in the treatment or prevention of pain including, for example, bone and joint pain (osteoarthritis), repetitive motion pain, dental pain, cancer pain, myofascial pain (muscular injury, fibromyalgia), perioperative pain (general surgery, gynecological) and chronic pain by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

In particular, inflammatory pain such as, for example, inflammatory airways disease (chronic obstructive pulmonary disease) would be effectively treated by the compounds of this invention by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

Further, the compounds of this invention can additionally be used to treat asthma, inflammatory bowel disease, rhinitis, pancreatitis, cystitis (interstitial cystitis), uveitis, inflammatory skin disorders, rheumatoid arthritis and edema resulting from trauma associated with burns, sprains or fracture by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

They may be used subsequent to surgical intervention (e.g. as post-operative analgesics) and to treat inflammatory pain of varied origins (e.g. osteoarthritis, rheumatoid arthritis, rheumatic disease, teno-synovitis and gout) as well as for the treatment of pain associated with angina, menstruation or cancer by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

They may be used to treat diabetic vasculopathy, post capillary resistance or diabetic symptoms associated with insulitis (e.g. hyperglycemia, diuresis, proteinuria and increased nitrite and kallikrein urinary excretion) by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg,

0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

They may be used to treat inflammatory skin disorders such as psoriasis and eczema by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

They may be used as smooth muscle relaxants for the treatment of spasm of the gastrointestinal tract or uterus or in the therapy of Crohn's disease, ulcerative colitis or pancreatitis by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

Such compounds may be used therapeutically to treat hyperreactive airways and to treat inflammatory events associated with airways disease e.g. asthma, and to control, restrict or reverse airways hyperreactivity in asthma by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

They may be used to treat intrinsic and extrinsic asthma including allergic asthma (atopic or non-atopic) as well as exercise-induced broncho-constriction, occupational asthma, viral or bacterial exacerbated asthma, other non-allergic asthmas and "wheezy-infant syndrome" by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

They may also be effective against pneumoconiosis, including aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis was well as adult respiratory distress syndrome, chronic obstructive pulmonary or airways disease, bronchitis, allergic rhinitis, and vasomotor rhinitis by

the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

Additionally, they may be effective against liver disease, multiple sclerosis, atherosclerosis, Alzheimer's disease, septic shock e.g. as anti-hypovolemic and/or anti-hypotensive agents, cerebral edema, headache including cluster headache, migraine including prophylactic and acute use, closed head trauma, irritable bowel syndrome and nephritis by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

Combination Therapy

Compounds of Formula I may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compounds of Formula I are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I. When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of Formula I is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of Formula I. Examples of other active ingredients that may be combined with a compound of Formula I, either administered separately or in the same pharmaceutical compositions, include, but are not limited to:
(1) morphine and other opiate receptor agonists including propoxyphene (Darvon); (2) non-steroidal antiinflammatory drugs (NSAIDs) including COX-2 inhibitors such as propionic acid derivatives (alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid, and tioxaprofen), acetic acid derivatives (indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac), fenamic

acid derivatives (flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid), biphenylcarboxylic acid derivatives (diflunisal and flufenisal), oxicams (isoxicam, piroxicam, sudoxicam and tenoxican), salicylates (acetyl salicylic acid, sulfasalazine) and the pyrazolones (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone), and the coxibs (celecoxib, valecoxib, rofecoxib and etoricoxib); (3) corticosteroids such as betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone and triamcinolone; (4) histamine H1 receptor antagonists such as bromopheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripelennamine, hydroxyzine, methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine pyrilamine, astemizole, terfenadine, loratadine, cetirizine, desloratadine, fexofenadine and levocetirizine; (5) histamine H2 receptor antagonists such as cimetidine, famotidine and ranitidine; (6) proton pump inhibitors such as omeprazole, pantoprazole and esomeprazole; (7) leukotriene antagonists and 5-lipoxygenase inhibitors such as zafirlukast, montelukast, pranlukast and zileuton; (8) drugs used for angina, myocardial ischemia including nitrates such as nitroglycerin and isosorbide nitrates, beta blockers such as atenolol, metoprolol, propranolol, acebutolol ,betaxolol, bisoprolol, carteolol, labetalol, nadolol, oxprenolol, penbutolol, pindolol, sotalol and timolol, and calcium channel blockers such as diltiazam, verapamil, nifedipine, bepridil, felodipine, flunarizine, isradipine, nicardipine and nimodipine; (9) incontinence medications such as antimuscarinics, e.g., tolterodine and oxybutinin); (10) gastrointestinal antispasmodics (such as atropine, scopolamine, dicyclomine, antimuscarinics, as well as diphenoxylate); skeletal muscle relaxants (cyclobenzaprine, carisoprodol, chlorphenesin, chlorzoxazone, metaxalone, methocarbamol, baclofen, dantrolene, diazepam, or orphenadrine); (11) gout medications such as allopurinol, probenicid and colchicine; (12) drugs for rheumatoid arthritis such as methotrexate, auranofin, aurothioglucose and gold sodium thiomalate; (13) drugs for osteoporosis such as alendronate and raloxifene; decongestants such as pseudoephedrine and phenylpropanolamine; (14) local anesthetics; (15) anti-herpes drugs such as acyclovir, valacyclovir and famcyclovir; and (15) anti-emetics such as ondansetron and granisetron.

Biological Evaluation

Assessing the Affinity of Selected Compounds to Bind to the Bradykinin B1 or B2 Receptor

Radioligand binding assays are performed using membranes from CHO cells that stably express the human, rabbit, rat, or dog B1 receptors or CHO cells that express the human B2 receptor. For all receptor types, cells are harvested from culture flasks in PBS/1mM EDTA and centrifuged at 1000xg for 10 minutes. The cell pellets are homogenized with a polytron in ice cold 20mM HEPES, 1mM EDTA, pH 7.4 (lysis buffer) and centrifuged at 20,000xg for 20 minutes. The membrane pellets are rehomogenized in lysis buffer, centrifuged again at 20,000xg and the final pellets are resuspended at 5mg protein/ml in assay buffer (120mM NaCl, 5mM KCl, 20mM HEPES, pH 7.4) supplemented with 1% BSA and frozen at –80°C.

On the day of assay, membranes are centrifuged at 14,000xg for 5 minutes and resuspended to the desired protein concentration in assay buffer containing 100nM enaliprilat, 140μg/mL bacitracin and 0.1% BSA. 3H-des-arg10, leu9 kallidin is the radioligand used for the human and rabbit B1 receptors, 3H-des-arg10 kallidin is used for the rat and dog B1 receptors, and 3H-bradykinin is used to label the human B2 receptor.

For all assays, compounds are diluted from DMSO stock solutions with 4μL added to assay tubes for a final DMSO concentration of 2%. This is followed by the addition of 100μL radioligand and 100μL of the membrane suspension. Nonspecific binding for the B1 receptor binding assays is determined using 1μM des-arg10 kallidin and nonspecific binding for the B2 receptor is determined with 1μM bradykinin. Tubes are incubated at room temperature (22°C) for 60 minutes followed by filtration using a Tomtec 96-well harvesting system. Radioactivity retained by the filter is counted using a Wallac Beta-plate scintillation counter.

The compounds of this invention have affinity for the B1 receptor in the above assay as demonstrated by results of less than 5μM. It is advantageous that the assay results be less than 1μM, even more advantageous for the results be less than 0.5μM. It is further advantageous that compounds of this invention have affinity for the bradykinin B1 receptor over the bradykinin B2 receptor; more advantageously, the affinity for the B1 receptor is at least 10 fold, and preferably over 100 fold, over that for the B2 receptor.

Assay for Bradykinin B1 Antagonists

B1 agonist-induced calcium mobilization was monitored using a Fluorescence Imaging Plate Reader (FLIPR). CHO cells expressing the B1 receptor were plated in 96 or 384 well plates and allowed to incubate in Iscove's modified DMEM overnight. Wells were washed two times with a physiological buffered salt solution and then incubated with 4uM Fluo-3 for one hour at 37°C. The plates were then washed two times with buffered salt solution and 100uL of buffer was added to each well. Plates were placed in the FLIPR unit and allowed to equilibrate for two minutes. The test compound was then added in 50ul volumes followed five minutes later by 50ul of agonist (des-arg^{10} kallidin). Relative fluorescence peak heights in the absence and presence of antagonist were used to calculate the degree of inhibition of the B1 receptor agonist response by the test compound. Eight to ten concentrations of test compound were typically evaluated to construct an inhibition curve and determine IC50 values using a four-parameter nonlinear regression curve fitting routine.

Assay for Bradykinin Inverse Agonists

Inverse agonist activity at the human B1 receptor was evaluated using transiently transfected HEK293 cells. One day following transfection cell flasks were labeled overnight with 6uCi/ml [^{3}H]myo-inositol. On the day of assay, the media was removed and the attached cells were gently rinsed with 2x20ml of phosphate-buffered saline. Assay buffer (HEPES buffered physiological salts, pH 7.4) was added and the cells were detached by tapping of the flask. The cells were centrifuged at 800xg for five minutes and resuspended at 1x10^6 cells/ml in assay buffer supplemented with 10mM lithium chloride. After 10 minutes at room temperature, one-half ml aliquots were distributed to tubes containing test compound or vehicle. After an additional 10 minutes the tubes were transferred to a 37°C water bath for 30 minutes. The incubation was terminated by the addition of a 12% perchloric acid solution and the tubes were placed on ice for 30 minutes. The acid was then neutralized with KOH and the tubes centrifuged to pellet precipitated material. [^{3}H]Inositol monophosphate formed was recovered by standard ion exchange chromatographic techniques and quantitated by liquid scintillation counting. Inverse agonist activity was determined by the degree to which a test compound reduced basal (cells incubated with vehicle) levels of [^{3}H]inositol monophosphate accumulation.

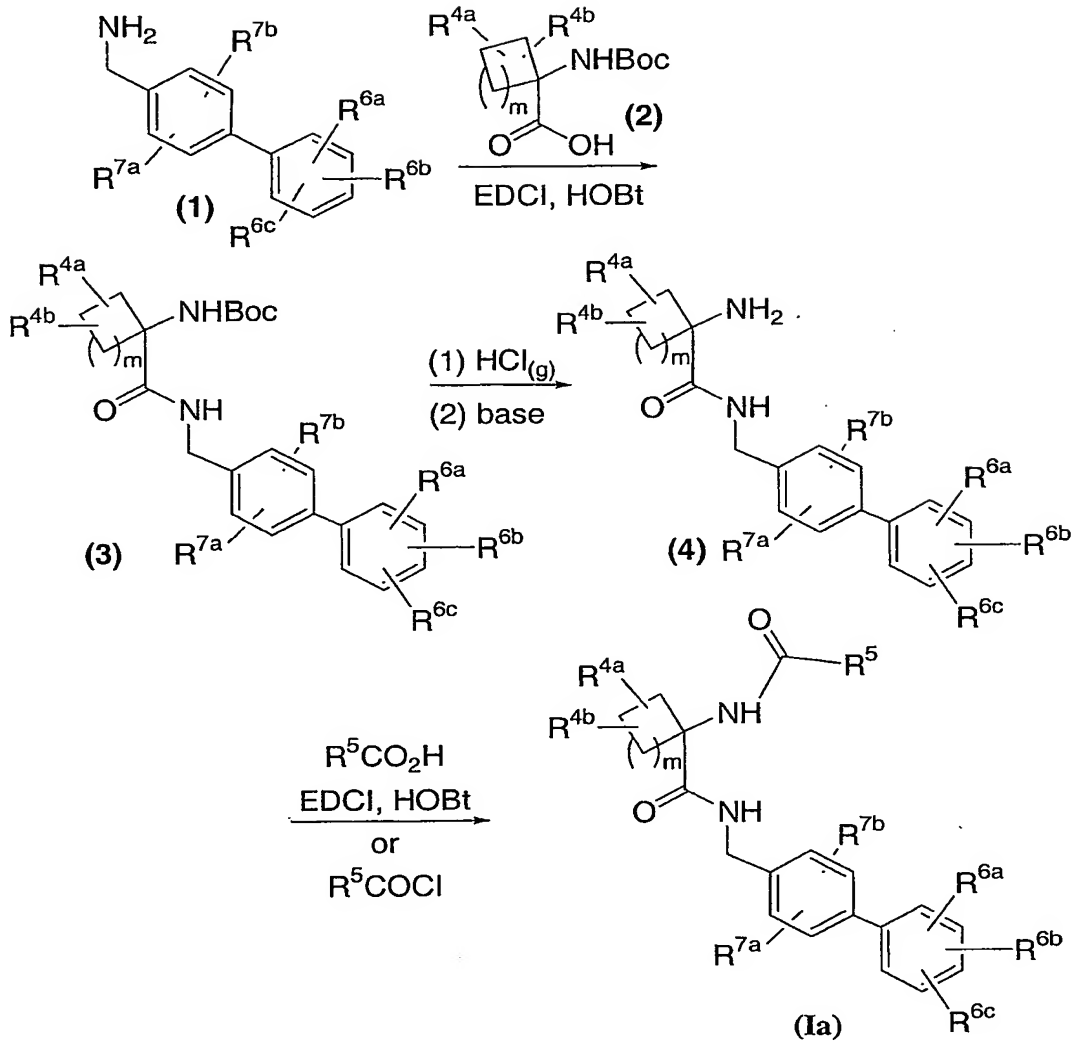
Abbreviations Used

The following abbreviations have the meanings indicated, unless stated otherwise in the specification:

BOC (boc)	t-butyloxycarbonyl
DCM	dichloromethane
DMF	dimethylformamide
DMSO	Dimethyl sulfoxide
EDC or EDCI	1-(3-dimethylaminopropyl)3-ethylcarbodiimide HCl
eq.	equivalent(s)
ES (or ESI) - MS	electron spray ionization - mass spectroscopy
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
FAB-MS	fast atom bombardment-mass spectroscopy
HOBt	1-hydroxybenzotriazole hydrate
HPLC	high pressure liquid chromatography
LCMS	Liquid chromatography/mass spectroscopy
LHMDS	lithium bis(trimethylsilyl)amide
Me	methyl
MeOH	Methanol
MHz	megahertz
MsCl	Mesyl chloride
NEt_3	Triethylamine
NMR	nuclear magnetic resonance
TFA	trifluoroacetic acid
THF	tetrahydrofuran

Compounds of formula I may be prepared according to the following illustative schemes.

SCHEME 1

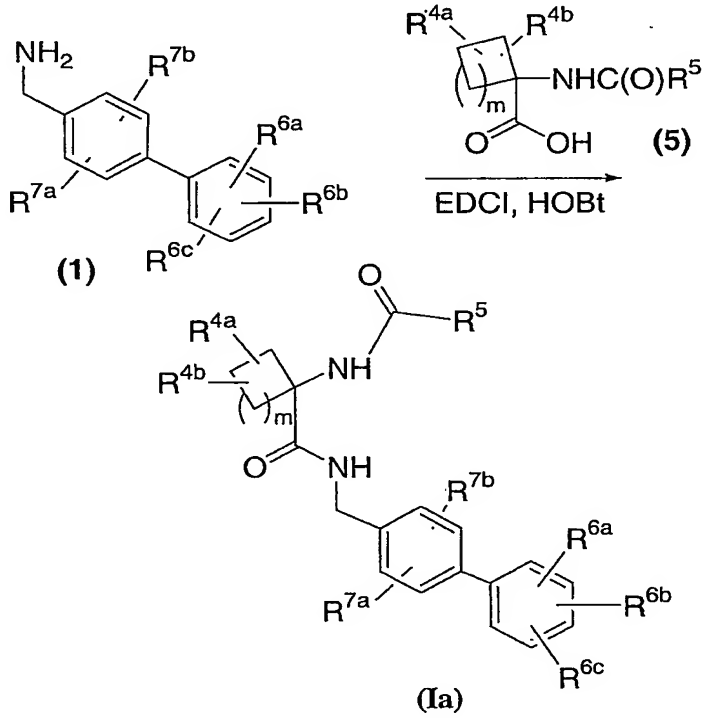


In Scheme 1, compound (Ia) is assembled by coupling the biarylmethanamine derivative (1) to the protected aminocycloalkanoic acid (2) using standard peptide coupling reagent combinations, such as EDCI/HOBt, in an appropriate solvent, such as THF, to provide (3). The Boc protecting group is then removed by the action of an acid, like HCl, in an appropriate solvent, like MeOH, to yield an ammonium salt from which the free-base derivative (4) may be obtained using an appropriate base, such as ammonia, and an appropriate solvent, such as

chloroform. This amine derivative (4) is then reacted with a carboxylic acid or carboxylic acid equivalent to yield title compound (Ia). Alternatively, the acid-salt of (4) can be used in the final reaction to yield title compound (Ia) provided an appropriate base such as triethylamine is added.

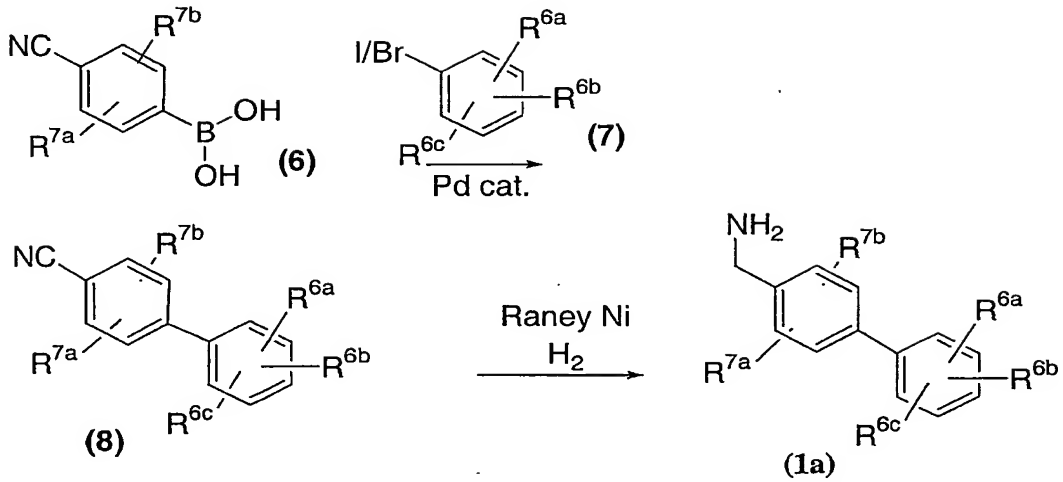
Alternatively, compound (Ia) may be assembled by coupling the biarylmethanamine derivative (1), with the acylated aminocycloalkanoic acid (5) as shown in Scheme 1a.

SCHEME 1a



A number of synthetic strategies may be employed to assemble the intermediate biarylmethanamine derivative (1) as shown in Schemes 2a-2c.

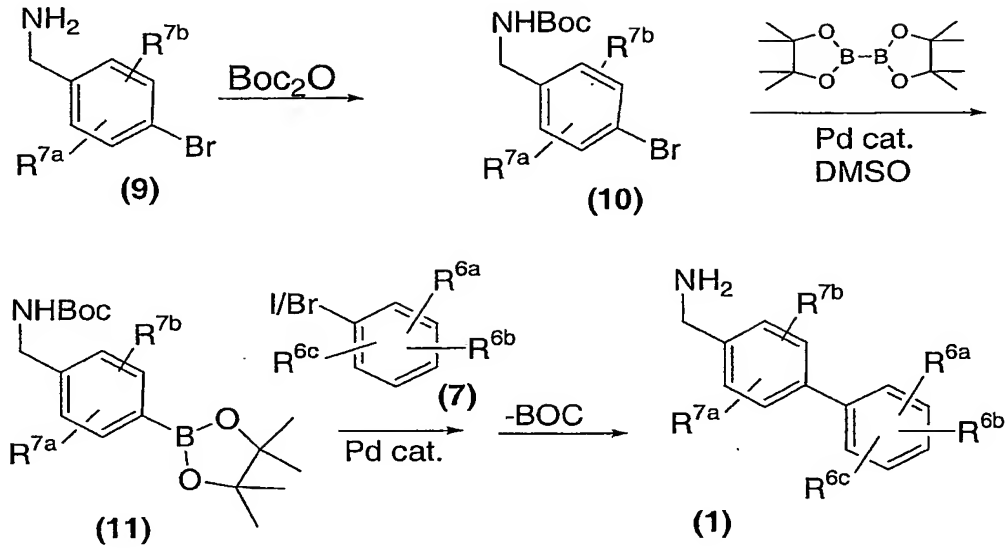
SCHEME 2a



In Scheme 2a, the cyanobiaryl derivative (8) is assembled using a Suzuki reaction between an aromatic boronic acid derivative (6), or an appropriate boronic ester derivative, and an aromatic halide (7) in the presence of a triarylphosphine, like triphenylphosphine, and a metal catalyst, like palladium acetate. The resultant cyano biaryl intermediate (8) is then catalytically reduced to the corresponding amine biaryl derivative (1a) using hydrogen and a metal, such as Raney Ni, in an appropriate solvent.

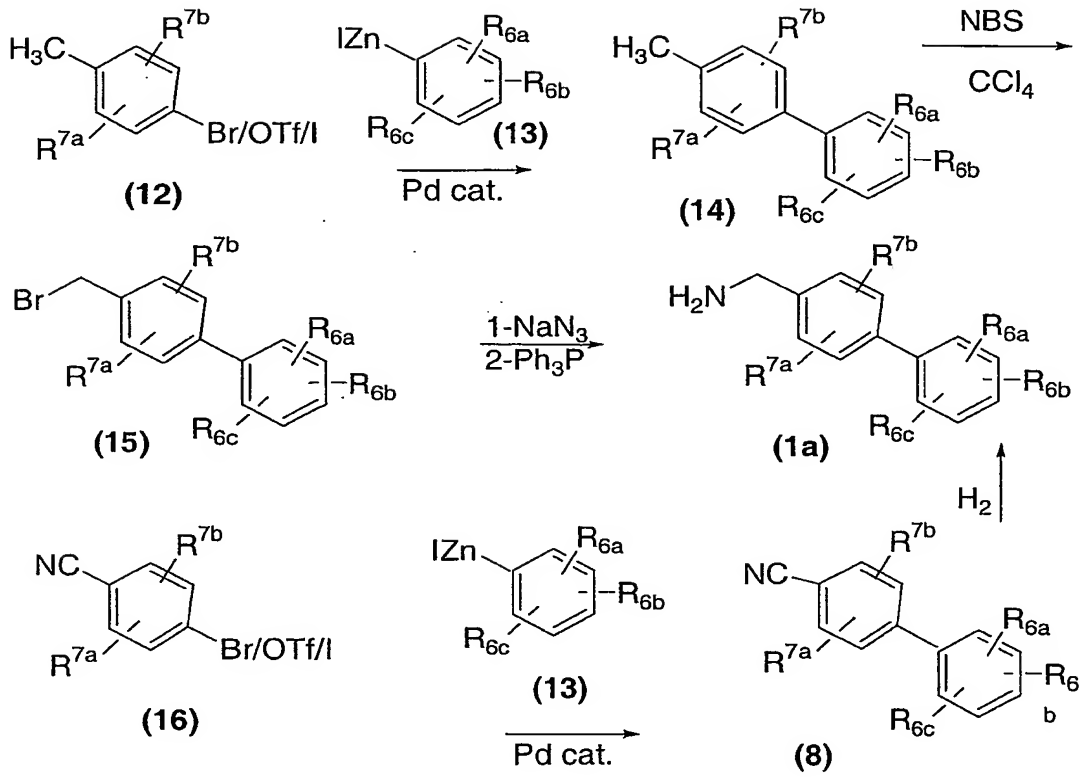
Alternatively, as illustrated in Scheme 2b, a methanamine derivative (9), after primary amine protection with an appropriate protecting group such as Boc, is elaborated to the pinacol boron ester (11) using a palladium catalyst in an appropriate solvent, like dimethyl sulfoxide. This boron ester (11) is coupled to an aryl halide derivative (7) employing Suzuki reaction conditions to yield (1).

SCHEME 2b



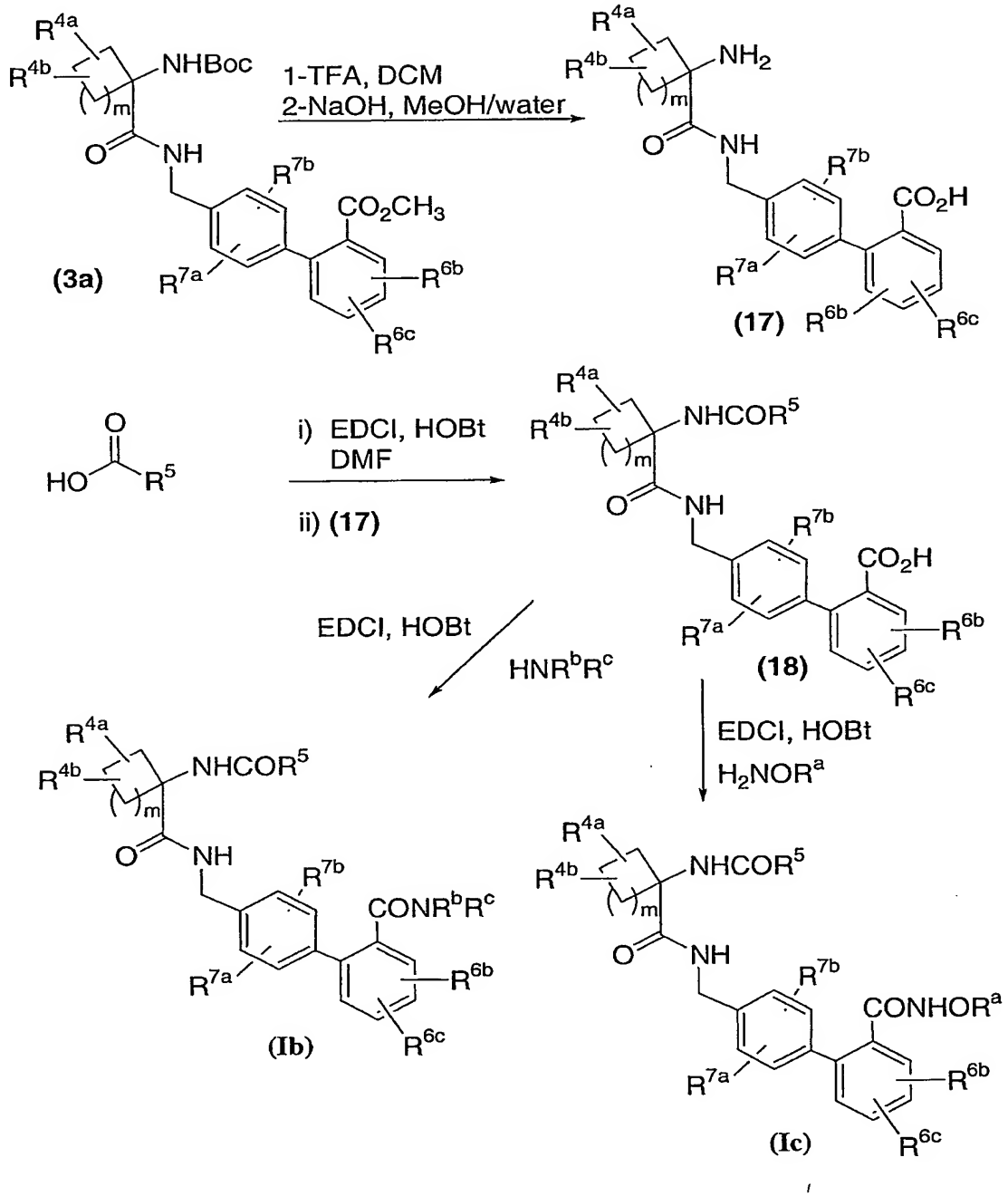
A third method for the preparation of biarylmethanamine derivatives is depicted in Scheme 2c. The biaryl moiety (14) is first assembled using a palladium catalyzed coupling of (12) with an aryl zinc compound (13) as shown. The methyl group of biaryl (14) is then elaborated according to the three step sequence of halogenation, nucleophilic displacement of the halogen with azide, and reduction to provide the corresponding amine intermediate (1a). Alternatively, the biarylmethanamine (1a) can also be prepared starting from the arylcarbonitrile (16) and aryl zinc compuond (13) as previously discussed. The resulting biarylcarbonitrile (8) is then reduced using hydrogen to provide (1a).

SCHEME 2c



It will be appreciated by persons skilled in the art that functional group interconversion can be used to provide various compounds of formula I. As illustrated in Scheme 3, derivative (3a) is bis-deprotected first by the action of a strong acid, like TFA, and second by alkaline hydrolysis in a suitable mixture of water and an organic solvent, like methanol, at a temperature between 25 and 100 °C to yield the amino acid derivative (17). Prior activation of a carboxylic acid (R^5COOH) with an appropriate set of peptide coupling reagents, like EDCI/HOBt, forms the 'active ester' which then reacts with the amino acid derivative (17) to yield (18). The latter compound can either react with amines (HNR^bR^c) or alkyloxy amines (H_2NOR^a) under the action of an appropriate set of peptide coupling reagents, like EDCI/HOBt, to form the claimed compounds (Ib) and (Ic), respectively.

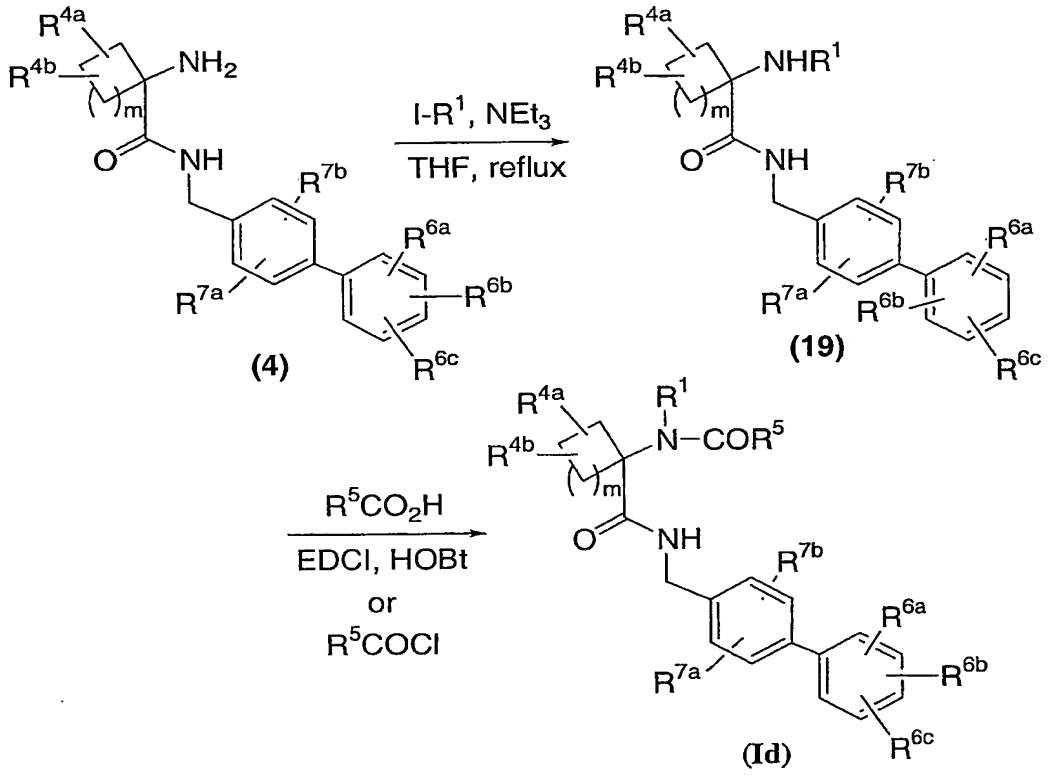
SCHEME 3



N-alkylation is illustrated in Scheme 4. The amine (4) is alkylated with excess alkyl iodide (I-R1) in an appropriate solvent, like THF, in the presence of

an acid scavenger, like triethylamine, at elevated temperatures to provide (19), along with bis-alkylated material. Secondary amine (19) is then converted to the title compound by reacting with a carboxylic acid or carboxylic acid equivalent to provide (Id).

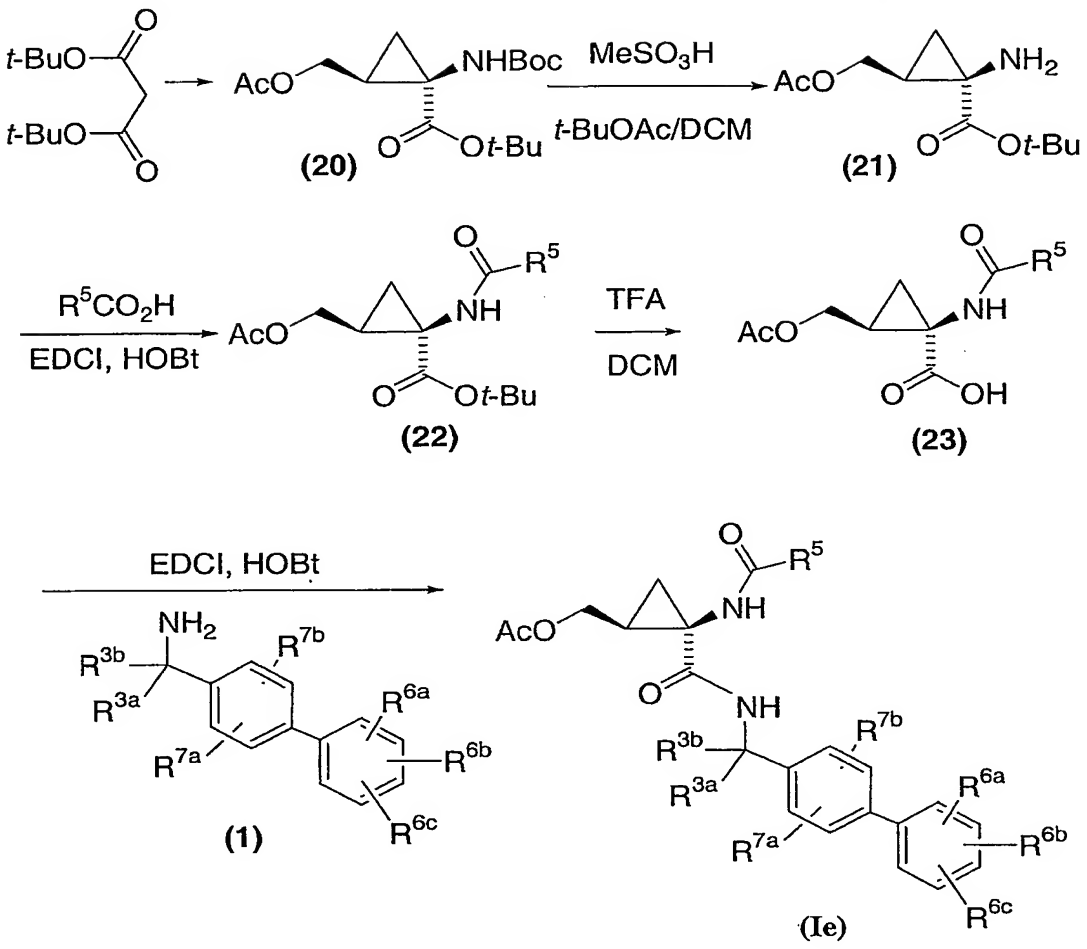
SCHEME 4



The preparation of compounds of formula I having a 1,2-cis- or 1,2-trans-cyclopropyl moiety is illustrated in Schemes 5 and 6. According to known procedures (K. Burgess et al., *J. Org. Chem.*, 57:5931-5936(1992)), di-*tert*-butyl malonate is elaborated to derivative (20). The N-Boc group is removed using methane sulfonic acid according to L. S. Lin et al. *Tetrahedron Lett.*, 41:7013-7016(2000) to give amine (21). This amine is allowed to react with a carboxylic acid or carboxylic acid equivalent under appropriate peptide coupling conditions to yield (22). The *tert*-butyl ester is then cleaved with an acid, like TFA, in an appropriate solvent, like DCM, to provide acid (23). Biarylmethanamine (1) is then coupled with the acid (23)

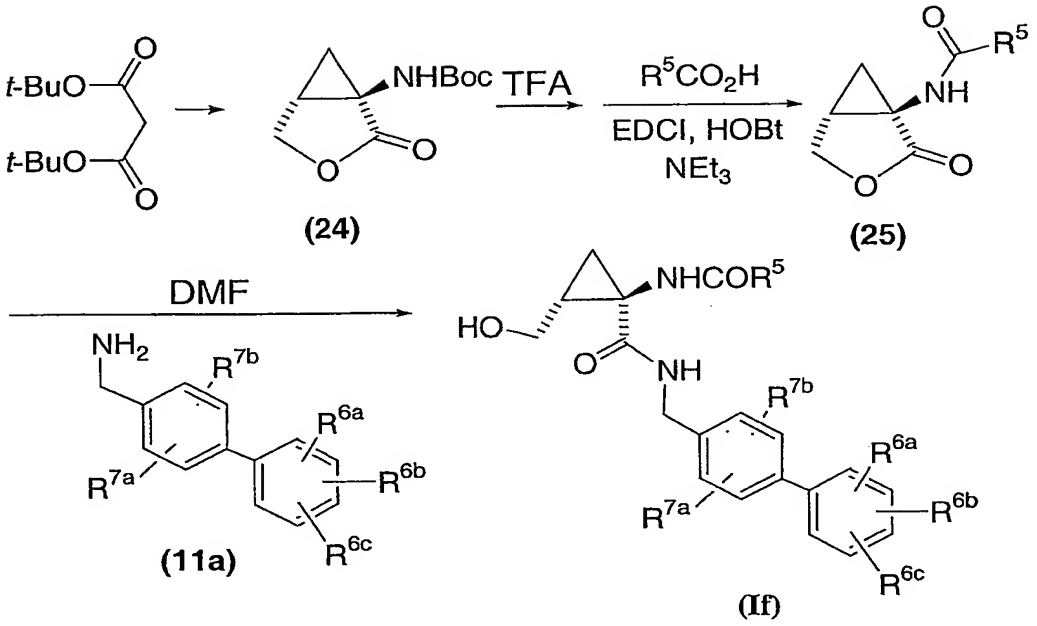
using an appropriate set of peptide coupling reagents, like EDCI/HOBt, to produce the title compound (Ie). Further elaboration of (Ie) to additional compounds of formula I may be accomplished using procedures well known to those skilled in the art. For example, the acetyl group may be removed by hydrolysis to provide the corresponding alcohol; the alcohol may be converted to the corresponding sulfonate by treatment with sulfonyl chloride, and the sulfonate may be converted to the corresponding halide by treatment with a source of the halide. These and other functional transformations to provide compounds of formula I are described in typical organic chemistry textbooks such as March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 5th Ed., John Wiley & Sons, 2000.

SCHEME 5



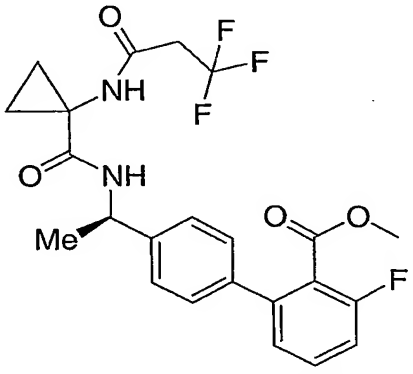
In Scheme 6, according to known procedures (K. Burgess et al., *J. Org. Chem.*, 57:5931-5936(1992)), di-*tert*-butyl malonate is elaborated to derivative (24). The N-Boc group is removed using an acid, like TFA, in an appropriate solvent, like DCM. This amine is allowed to react with a carboxylic acid or carboxylic acid equivalent under appropriate peptide coupling conditions, like EDCI/HOBt/NEt3 to yield (25). Biarylmethanamine (1), is then allowed to open the lactone (25) in an appropriate aprotic solvent, like DMF, at a temperature between 20 and 100 °C, to produce the title compound (If). Further elaboration of (If) to additional title compounds may be accomplished using procedures well known to those skilled in the art as previously discussed.

SCHEME 6



REFERENCE PROCEDURE 1

Methyl 3-fluoro-4'-{(1R)-1-[({1-[(3,3,3-trifluoropropanoyl)amino]cyclopropyl}-carbonyl)amino]ethyl}-1,1'-biphenyl-2-carboxylate



Commercially available (1R)-1-(4-bromophenyl)ethanamine was Boc protected, using standard procedures known to those skilled in the art, to produce tert-butyl (1R)-1-(4-bromophenyl)ethylcarbamate.

To a solution of tert-butyl (1R)-1-(4-bromophenyl)ethylcarbamate (7.6 g, 25.3 mmol) in DMSO (20 mL) was added bis(pinacolato)diboron (7.07 g, 27.9 mmol), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloro-methane adduct (2.06 g, 2.53 mmol), and potassium acetate (7.45 g, 76.0 mmol) at room temperature under N_2. The resulting mixture was heated at 80 °C for 1 hour. The reaction was quenched by addition of EtOAc and filtered through celite. The organic extract was washed with water three times, saturated NaCl, dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified on silica gel eluted with 0-20% ethyl acetate in hexane to provide *tert*-butyl (1R)-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethylcarbamate as a clear light yellow oil with a mass ion (ES+) of 333.

To a stirred solution of *tert*-butyl (1R)-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethylcarbamate (1.0 g, 2.9 mmol) and methyl 2-fluoro-6-iodobenzoate (1.2 g, 4.32 mmol) in 25 mL of a 5:1 THF:water mixture was added potassium carbonate (1.2 g, 8.64 mmol), tri-*o*-tolylphosphine (350 mg, 1.15 mmol) and lastly palladium acetate (65 mg, 0.29 mmol). The reaction vessel was then sealed and placed into a 90 °C oil bath for overnight stirring and heating. After about 18 hours the reaction mixture was cooled to ambient temperature and then diluted with EtOAc. The organics were washed with brine (x4), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give an oil. This oil was subject to silica gel chromatography eluting with 10-60% EtOAc in hexanes to provide methyl 4'-{(1R)-1-[(*tert*-butoxycarbonyl)amino]ethyl}-3-fluoro-1,1'-biphenyl-2-carboxylate (205 mg), found to be pure by LC/MS and proton NMR.

Methyl 4'-{(1R)-1-[(*tert*-butoxycarbonyl)amino]ethyl}-3-fluoro-1,1'-biphenyl-2-carboxylate (205 mg, 0.60 mmol) dissolved in MeOH (15 mL) was cooled to 0 °C. This homogenous solution was saturated with anhydrous hydrogen chloride and allowed to sit for 20 minutes. Dry nitrogen was then bubbled through the solution for about 30 minutes. Solvent was then removed under reduced pressure to yield an oily residue. The oil was then dissolved in DCM and the solvent removed. This process was repeated until a solid amine hydrochloride was obtained.

The above amine hydrochloride (85 mg, 0.27 mmol) along with 1-[(*tert*-butoxycarbonyl)amino]cyclopropanecarboxylic acid (55 mg, 0.27 mmol), $HOBt{\cdot}H_2O$ (8.4 mg, 0.05 mmol) and triethylamine (33 mg, 0.33 mmol) were dissolved in 4.5 mL of THF. To this room-temperature solution was added EDCI (74 mg, 0.38 mmol). After overnight stirring (*ca.* 16.5 h) the reaction mixture was diluted

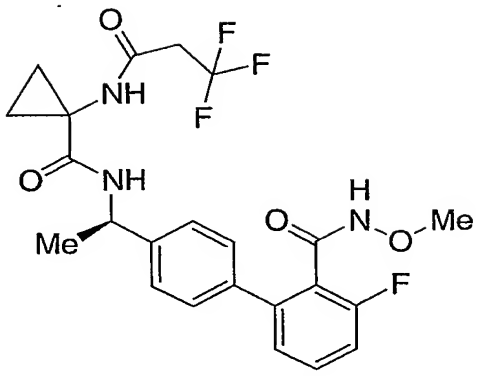
with water and EtOAc. The organic layer was washed successively with 1N HCl, 5% sodium bicarbonate, half-brine (x3) and then brine. The organic layer was dried over sodium sulfate, filtered and evaporated under reduced pressure to obtain a residue which was subjected to silica gel chromatography eluting with 1-6% MeOH in DCM. Collection of product containing fractions and removal of solvent yielded 108 mg (86%) of methyl 4'-{(1R)-1-[({1-[(*tert*-butoxycarbonyl)amino]cyclopropyl}carbonyl)-amino]ethyl}-3-fluoro-1,1'-biphenyl-2-carboxylate.

Methyl 4'-{(1R)-1-[({1-[(*tert*-butoxycarbonyl)amino]cyclopropyl}-carbonyl)amino]ethyl}-3-fluoro-1,1'-biphenyl-2-carboxylate (108 mg, 0.24 mmol) dissolved in MeOH (5.0 mL) was cooled to 0 °C. This homogenous solution was saturated with anhydrous hydrogen chloride and allowed to sit for 30 minutes. Dry nitrogen was then bubbled through the solution for about 50 min. Solvent was then removed under reduced pressure to yield an oily residue. The oil was then dissolved in DCM and the solvent removed. This process being repeated until a solid amine hydrochloride was obtained.

The above amine hydrochloride (46 mg, 0.12 mmol) along with trifluoropropionic acid (15 mg, 0.12 mmol), HOBt•H_2O (3.6 mg, 0.02 mmol) and triethylamine (14 mg, 0.14 mmol) were dissolved in 1.6 mL of THF plus 1.6 mL of DMF. To this room-temperature solution was added EDCI (31 mg, 0.16 mmol). After overnight stirring (*ca.* 18 h) the reaction mixture was diluted with water and EtOAc. The organic layer was washed successively with 1N HCl, 5% sodium bicarbonate, half-brine (x3) and then brine. The organic layer was dried over sodium sulfate, filtered and evaporated under reduced pressure to obtain a residue which was subjected to silica gel chromatography eluting with 1-12% MeOH in DCM. Collection of product containing fractions and removal of solvent yielded 36 mg (67%) of the title compound as a foaming solid. Purity was determined by LCMS (ES MS, $M+H^+$ found:467) and proton NMR (400 MHz, CD_3OD : δ 7.555, 7.540, 7.535, 7.520, 7.515, 7.500, 7.393, 7.373, 7.319, 7.302, 7.298, 7.240, 7.222, 7.221, 7.211, 7.188, 7.167, 7.165, 5.116, 5.099, 5.081, 5.064, 3.659, 3.268, 3.241, 3.214, 3.187, 1.508, 1.490, 1.483, 1.477, 1.474, 1.470, 1.465, 1.454, 1.444, 1.056, 1.049, 1.036, 1.031, 1.023, 1.007, 0.999, 0.995, 0.982, 0.974).

REFERENCE PROCEDURE 2

3-Fluoro-N-methoxy-4'-{(1R)-1-[({1-[(3,3,3-trifluoropropanoyl)amino]cyclopropyl}-carbonyl)amino]ethyl}-1,1'-biphenyl-2-carboxamide



A solution of methyl 4'-{(1R)-1-[({1-[(*tert*-butoxycarbonyl)amino]-cyclopropyl}carbonyl)amino]ethyl}-3-fluoro-1,1'-biphenyl-2-carboxylate (466 mg, 1.0 mmol) in DCM (15 mL) and TFA (15 mL) was stirred under N_2 for 20 minutes at ambient temperature, then the organic solvent was removed under vacuum. The residue was dissolved in MeOH (20 mL), 4N NaOH (10 mL) and water (10 mL). This mixture was heated at reflux for 4 hours and then neutralized with 6N HCl. Purification was achieved by preparative HPLC on a delta-pack C_{18} column, 300 Å, pore size 15 μM with 0.05% HCl acid -aqueous acetonitrile solvent systems using various linear gradients. Fractions containing product of 99% purity as measured by HPLC were combined and lyophilized to give 4'-((1R)-1-{[(1-aminocyclopropyl)-carbonyl]amino}ethyl)-3-fluoro-1,1'-biphenyl-2-carboxylic acid as a white solid.

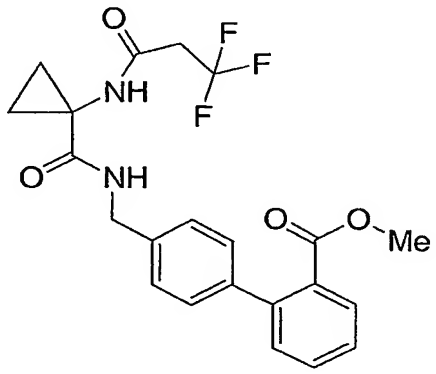
To a solution of trifluoropropionic acid (128 mg, 1.0 mmol) in DCM (1 mL), 1-ethyl-(3-dimethylaminopropyl)carbodiimide hydrochloride (229 mg, 1.2 mmol) and 1-hydroxy-7-azabenzotriazole (136 mg, 1.0 mmol) were added. The resulting solution was stirred at room temperature for 20 minutes, then 4'-((1R)-1-{[(1-aminocyclopropyl)carbonyl]amino}ethyl)-3-fluoro-1,1'-biphenyl-2-carboxylic acid (171 mg, 0.5 mmol) in 1mL DCM was added, followed by *N,N*-diisopropylethyl-amine until pH = 10 was achieved. The reaction mixture was stirred at ambient temperature under N_2 for 2 hours, concentrated under vacuum and then partitioned between water and ethyl acetate. The organic extract was washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluted with 40% MeOH in $CHCl_3$. Collection and concentration of appropriate fractions provided 3-fluoro-4'-{(1R)-1-[({1-[(3,3,3-trifluoropropanoyl)amino]cyclopropyl}carbonyl)-amino]ethyl}-1,1'-biphenyl-2-carboxylic acid as a white powder.

To a solution of the above acid (226 mg, 0.50 mmol) in DCM (1 mL), 1-ethyl-(3-dimethylaminopropyl)carbodiimide hydrochloride (134 mg, 0.70 mmol), 1-hydroxy-7-azabenzotriazole (68mg, 0.50 mmol) and methoxyamine hydrochloride (167 mg, 1.0 mmol) were added, followed by *N,N*-diisopropylethylamine until pH = 10 was achieved. The resulting solution was stirred at room temperature for 2 hours, and then partitioned between ethyl acetate and water. The organic extract was washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum. Purification was achieved by preparative HPLC on a delta-pack C_{18} column with 0.05% HCl acid -aqueous acetonitrile solvent systems using various linear gradients. Fractions containing product of 99% purity as measured by HPLC were combined and lyophilized to give the title compound as a white solid. . Purity was determined by LCMS (ES MS, $M+H^+$ found:482) and proton NMR (400 MHz, DMSO-d_6) δ 1.40 (d, J = 7.1 Hz, 3H), 0.60-0.80 (m, 2H), 1.27 (m, 2H), 3.23 (m, J = 11.2 Hz, 2H). 3.44 (s, 3H), 5.02 (q, J = 8 Hz, 1H), 7.25-7.39 (m, *6H),* 7.52 (m, 1H), 7.93 (d, J = 8.2Hz, 1H), 8.89 (s, 1H).

The following examples are provided to illustrate the invention without limiting the invention to the particulars of these examples. Compounds were named using: ACD/Name version 4.53 (Advanced Chemistry Development Inc. © 1994-2000). Address: 90 Adelaide Street West, Toronto, Ontario, M5H 3V9, Canada.

EXAMPLE 1

Methyl 4'-{[({1-[(3,3,3-trifluoropropanoyl)amino]cyclopropyl}carbonyl)amino]-methyl}-1,1'-biphenyl-2-carboxylate



To 500 mL of THF was added water (18.4 mL, 1.02 mol), potassium carbonate (70.5 g, 0.510 mol), methyl 2-iodobenzoate (53.5 g, 0.204 mol), 4-cyano-phenylboronic acid (30.0 g, 0.204 mol) and bis-(tri-o-tolylphosphine) palladium (II) chloride (1.65 g, 2.04 mmol). This mixture was heated to reflux for 3.5 hours and then cooled to ambient temperature for continued stirring overnight. The solvent was then removed under reduced pressure prior to dilution with EtOAc/water. The organic layer was extracted with additional EtOAc. The combined organics were washed with water, then brine. The organics were then dried over sodium sulfate, filtered, and then concentrated to obtain the crude product. This crude product was passed through a silica pad, eluting with 8:1 heptane:EtOAc to get 41.6 grams of methyl 4'-cyano-1,1'-biphenyl-2-carboxylate.

To a stirred solution of methyl 4'-cyano-1,1'-biphenyl-2-carboxylate (50.0 g, 0.211 mol) in 2M ammonia in methanol (500 mL) was added approximately 5 teaspoons of a 50% aqueous slurry of Raney Nickel (Aldrich). The reaction vessel was purged with nitrogen and then flushed with hydrogen from a balloon. After 6 hours of stirring under a fresh balloon, the balloon was recharged and stirring was continued for an additional 3 hours. Nitrogen was bubbled through the solution for 15 minutes prior to filtration through a celite pad. Solvent was removed and 1 L of diethyl ether was added with stirring. This solution was filtered and the solvent removed. The residue was now dissolved in a 1:1 mixture of diethyl ether:EtOAc prior to introduction of anhydrous hydrogen chloride (until no additional precipitate forms). The solid was filtered and dried in a vacuum oven over the weekend; providing 56.1 grams of methyl 4'-(aminomethyl)-1,1'-biphenyl-2-carboxylate hydrochloride, which gave LC/MS and proton NMR spectra consistent with theory.

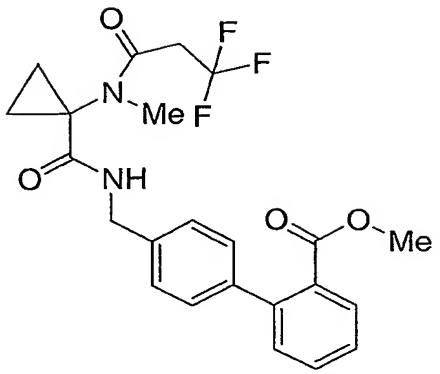
The free-base of the above mentioned amine hydrochloride (0.51 g, 2.1 mmol), was dissolved in anhydrous THF (21 mL). To this stirred solution was added 1-[(*tert*-butoxycarbonyl)amino]cyclopropanecarboxylic acid (0.51 g, 2.5 mmol), triethylamine (0.30 g, 3.0 mmol), HOBt•H_2O (65 mg, 0.42 mmol) and lastly EDCI (0.57 g, 3.0 mmol). This mixture was allowed to stir overnight. Solvent was then removed under reduced pressure and the residue was subjected to silica gel chromatography eluting with a 1-10% MeOH in DCM gradient to provide methyl 4'-{[({1-[(*tert*-butoxycarbonyl)amino]cyclopropyl}carbonyl)amino]methyl}-1,1'-biphenyl-2-carboxylate (0.84 g), giving LC/MS and proton NMR spectra consistent with theory.

Methyl 4'-{[({1-[(*tert*-butoxycarbonyl)amino]cyclopropyl}carbonyl)-amino]methyl}-1,1'-biphenyl-2-carboxylate (0.84 g, 2.0 mmol) dissolved in a mixture of DCM (3 mL) and MeOH (45 mL) was cooled to 0 °C. This homogenous solution was saturated with anhydrous hydrogen chloride and allowed to sit for 30 minutes. Dry nitrogen was then bubbled through the solution for about 30 min. Solvent was then removed under reduced pressure to yield an oily residue. The oil was then dissolved in DCM and the solvent removed. This process being repeated until a solid amine hydrochloride was obtained. Alteratively, the residue could be dissolved in chloroform followed by saturation with ammonia gas, filtration and solvent removal to obtain solid methyl 4'-({[(1-aminocyclopropyl)carbonyl]amino}methyl)-1,1'-biphenyl-2-carboxylate as the free-base.

To a room temperature, stirred solution of the above mentioned amine hydrochloride (0.15 g, 0.42 mmol) in DMF (2.8 mL) was added HOBt•H_2O (13 mg, 0.08 mmol), trifluoropropionic acid (64 mg, 0.50 mmol), triethylamine (100 mg, 1.0 mmol) and lastly EDCI (110 mg, 0.58 mmol). After overnight stirring (*ca.* 17 h) the reaction mixture was diluted with water and EtOAc. The organic layer was washed successively with 1N HCl, 5% sodium bicarbonate, half-brine (x3) and then brine. The organic layer was dried over sodium sulfate, filtered and evaporated under reduced pressure to obtain a residue which was subject to silica gel chromatography eluting with 1-12% MeOH in DCM. Collection of product containing fractions and removal of solvent yielded 141 mg (78%) of the title compound as a foaming solid. Purity was determined by LCMS (ES MS, M^++H_2O found:452) and proton NMR (400 MHz, CD_3OD : δ 7.748, 7.745, 7.729, 7.726, 7.560, 7.557, 7.541, 7.538, 7.446, 7.443, 7.427, 7.424, 7.380, 7.361, 7.323, 7.302, 7.238, 7.218, 4.461, 3.608, 3.249, 3.222, 3.195, 3.168, 1.532, 1.521, 1.513, 1.501, 1.048, 1.037, 1.029, 1.017).

EXAMPLE 2

Methyl 4'-{[({1-[methyl(3,3,3-trifluoropropanoyl)amino]cyclopropyl}carbonyl)-amino]methyl}-1,1'-biphenyl-2-carboxylate



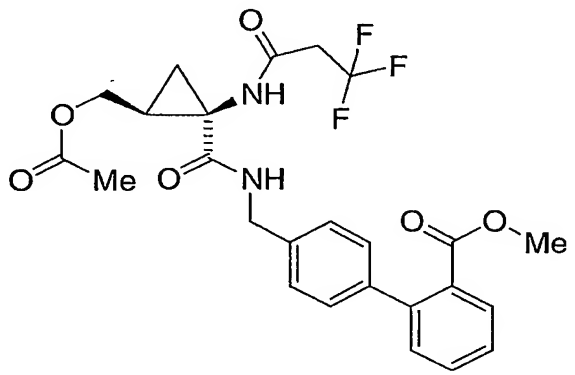
Methyl 4'-({[(1-aminocyclopropyl)carbonyl]amino}methyl)-1,1'-biphenyl-2-carboxylate (200 mg, 0.62 mmol), prepared according to Example 1, was dissolved in 5 mL of DCM along with iodomethane (130 mg, 0.93 mmol) and triethylamine (75 mg, 0.74 mmol). After no reaction was observed at ambient temperature, the reaction mixture was heated to reflux for about two days. After the first day, additional iodomethane was added (*ca.* 3-5 equiv.). After two days >50% of the starting material was consumed. The reaction mixture was concentrated under reduced pressure and the residue was subjected to silica gel chromatography eluting with 1-10% MeOH in DCM to afford 73 mg of methyl 4'-[({[1-(methylamino)cyclopropyl]carbonyl}amino)methyl]-1,1'-biphenyl-2-carboxylate.

The above secondary amine (73 mg, 0.22 mmol) along with trifluoropropionic acid (42 mg, 0.32 mmol) and HOBt•H_2O (40 mg, 0.26 mmol) were dissolved in a minimal amount of a 1:1 DCM:THF solution. To this room-temperature solution was added EDCI (54 mg, 0.28 mmol). After overnight stirring (*ca.* 18 h) the reaction was about 66% complete. Additional trifluoropropionic acid (42 mg), HOBt•H_2O (40 mg) and EDCI (54 mg) were added and the reaction mixture was allowed to stir for another day. Solvent was removed from the reaction mixture and the residue was subjected to silica gel chromatography eluting with 1-4% MeOH in DCM to obtain only partial purfication. A second attempt at silica gel chromatography eluting with 25-75% EtOAc in hexane, collection of product containing fractions and removal of solvent gave the title compound. Purity was determined by LCMS (ES MS, $M+H^+$ found:449) and proton NMR (400 MHz, $CDCl_3$(rotomers present) : δ 7.856, 7.837, 7.818, 7.557, 7.554, 7.538, 7.535, 7.519, 7.516, 7.439, 7.436, 7.420, 7.401, 7.357, 7.338, 7.305, 7.284, 7.269, 7.261 ($CHCl_3$), 7.249, 6.341, 4.526, 4.520, 4.512, 4.506, 4.495, 3.658, 3.356, 3.339, 3.330, 3.315, 3.291, 3.267, 3.256, 3.244, 3.232, 3.135, 3.048, 2.094, 2.085, 2.068, 2.059, 1.685,

1.667, 1.657, 1.640, 1.630, 1.318, 1.291, 1.279, 1.273, 1.260, 1.242, 1.238, 1.229, 1.221, 1.211, 1.194, 1.184).

EXAMPLE 3

Methyl 4'-{[({(±)-*cis*-(acetyloxy)methyl]-1-[(3,3,3-trifluoropropanoyl)amino]-cyclopropyl}carbonyl)amino]methyl}-1,1'-biphenyl-2-carboxylate



tert-Butyl(±)-*cis*-(acetyloxy)methyl]-1-[(tert-butoxycarbonyl)amino]-cyclopropane carboxylate (1.77 g, 5.38 mmol) was dissolved in 25 mL of *tert*-butyl acetate and 5.75 mL of methylene chloride. The solution was stirred at ambient temperature and 700 µL (10.8 mmol) methanesulfonic acid was added. After stirring overnight, TLC analysis (hexane-ethyl acetate, 75-25) indicated that no starting material remained. Saturated sodium bicarbonate solution was added to bring the pH of reaction mixture to 7.5 and the aqueous phase was extracted with ethyl acetate (3X75 mL). The combined organic extracts were dried (sodium sulfate) and concentrated to yield 523 mg of *tert*-butyl (±)-*cis*- (acetyloxy)methyl]-1-aminocyclo-propanecarboxylate.

The above amine (523 mg, 2.28 mmol) was mixed with 3,3,3-trifluoro-propionic acid (366 mg, 2.86 mmol) in 4.6 mL of *N,N*-dimethylformamide. *N*-Hydroxybenzotriazole (455 mg, 2.97 mmol) was added, followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (569 mg, 2.97 mmol). The pH of the reaction mixture was adjusted to 8.5 with triethylamine and the mixture was allowed to stir for 2 hours at ambient temperature. The reaction was treated with 20 ml of a 50 % sodium bicarbonate solution and was extracted with ethyl acetate (3X75 mL). The combined organic extracts were washed with water and brine, then dried (sodium sulfate) and concentrated in vacuo to give the crude product. This material was

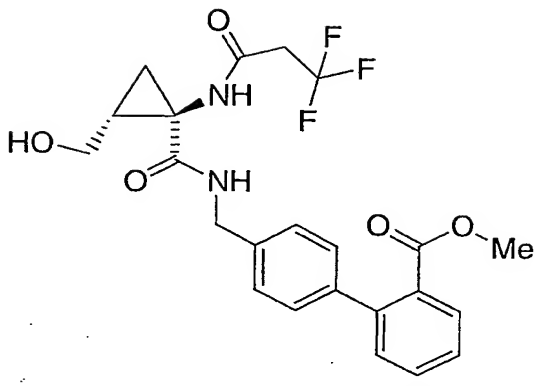
applied to a 35 g ISCO column and eluted with 5-20 % ethyl acetate in hexane to yield 500 mg (65%) of *tert*-butyl (±)-*cis*-(acetyloxy)methyl]-1-[(3,3,3-trifluoro-propanoyl)amino]cyclopropane carboxylate.

tert-Butyl (±)-*cis*-(acetyloxy)methyl]-1-[(3,3,3-trifluoropropanoyl)-amino]cyclopropane carboxylate (489 mg, 1.44 mmol) was dissolved in a mixture of 4 mL of methylene chloride and 1.22 mL of trifluoroacetic acid. The reaction mixture was allowed to stir at ambient temperature for 3.5 hours. The solvents were removed in vacuo and the residue was azeotroped with toluene (450 ml) to afford 408 mg of (±)-*cis*-(acetyloxy)methyl]-1-[(3,3,3-trifluoropropanoyl)amino] cyclopropane-carboxylic acid.

(±)-*cis*-(Acetyloxy)methyl]-1-[(3,3,3-trifluoropropanoyl)amino]-cyclopropane carboxylic acid (408 mg, 1.44 mmol) was mixed with methyl 4'-(aminomethyl)-1,1'-biphenyl-2-carboxylate (418 mg, 1.73 mmol) in 3 mL of *N,N*-dimethylformamide. *N*-Hydroxybenzotriazole (265 mg, 1.73 mmol) was added, followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (332 mg, 1.73 mmol). The mixture was adjusted to pH 8.5 with triethylamine and allowed to stir at room temperature for 2 hours. Water (10 mL) was added and the mixture was extracted with ethyl acetate (3X50 mL). The combined organic extracts were washed with water and dried (sodium sulfate), then concentrated in vacuo to afford 700 mg of the crude product. This material was chromatographed on silica gel to give 500 mg (69%) of title compound. Purity was determined by LCMS (ES MS, M+H+ found:507) and proton NMR (400 MHz, $CDCl_3$) δ 0.85–0.87 (dd, 1H), 1.92-1.95 (dd, 1H), 2.1-2.17 (m, 1H), 2.13 (s, 3H), 3.15 (dd, 2H, $\underline{CH_2}CF_3$), 3.66 (s, 3H), 4.0 (dd, 1H), 4.31 (dd, 1H), 4.49 (m, 2H, $\underline{CH_2}C_6H_4$-), 6.61 (dd, 1H, N<u>H</u>), 7.27 (m, 4H), 7.35 (d, 1H), 7.41 (ddd, 1H), 7.53 (ddd, 1H), 7.81 (d, 1H), 8.3 (s, 1H, N<u>H</u>).

EXAMPLE 4

Methyl 4'-{[({(±)-*trans*-2-(hydroxymethyl)-1-[(3,3,3-trifluoropropanoyl)amino]-cyclopropyl}carbonyl)amino]methyl}-1,1'-biphenyl-2-carboxylate



tert-Butyl (±)-*trans*-2-oxo-3-oxabicyclo[3.1.0]hex-1-ylcarbamate (241 mg, 1.13 mmol) was dissolved in a 3:1 mixture of methylene chloride:trifluoroacetic acid. The solution was stirred at ambient temperature for two hours. The solvents were removed in vacuo and the residue was taken up in 150 mL of ethyl acetate. The ethyl acetate solution was washed with a 50 % sodium bicarbonate solution and brine, then dried (sodium sulfate) and concentrated to afford 128 mg of (±)-*trans*-1-amino-3-oxabicyclo[3.1.0]hexan-2-one.

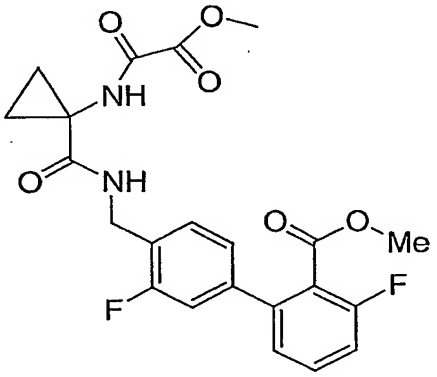
(±)-*Trans*-1-amino-3-oxabicyclo[3.1.0]hexan-2-one (128 mg, 1.13 mmol) was mixed with 3,3,3-trifluoropropionic acid in 2.3 mL of N,N-dimethyl-formamide. Hydroxybenzotriazole (17.4 mg, 0.11 mmol) was added followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (282 mg, 1.47 mmol). The pH of the reaction mixture was adjusted to 8.5 with triethylamine and the mixture was allowed to stir at ambient temperature for 2 hours. Water was then added and the reaction mixture was extracted with ethyl acetate. The combined organic extracts were washed with water and brine, then dried (sodium sulfate) and concentrated to give the crude product. This was purified by silica gel chromatography to afford 120 mg (45%) of 3,3,3-trifluoro-*N*-[(±)-*trans*-2-oxo-3-oxabicyclo[3.1.0]hex-1-yl]-propanamide.

3,3,3-Trifluoro-*N*-[(±)-*trans*-2-oxo-3-oxabicyclo[3.1.0]hex-1-yl]-propanamide (80 mg, 0.359 mmol) was dissolved in 700 µL of *N,N*-dimethyl-formamide under an inert atmosphere. Methyl 4'-(aminomethyl)-1,1'-biphenyl-2-carboxylate (95 mg, 0.395 mmol) was added and the mixture was heated to 60 °C. After 10 hours the mixture was concentrated to dryness. The residue was purified by silica gel chromatography (chloroform-methanol:94-6, v/v elution). This afforded 55 mg (35%) of the title compound. Purity was determined by LCMS (ES MS, M+H+ found:465) and proton NMR (400 MHz, $CDCl_3$) δ 1.21–1.24 (dd, 1H), 1.52-1.55

(dd, 1H), 1.6-1.7 (m, 2H), 3.05 (dd, 2H, $\underline{CH_2}CF_3$), 3.43 (m, 1H), 3.58 (br s, 1H, N$\underline{H}$), 3.67 (s, 3H), 3.96-3.99 (dd, 1H), 4.48 (m, 2H, $\underline{CH_2}C_6H_4$-), 7.26 (m, 4H), 7.34 (d, 1H), 7.41 (ddd, 1H), 7.47 (m, 1H, N$\underline{H}$), 7.53 (ddd, 1H), 7.83 (dd, 1H).

EXAMPLE 5

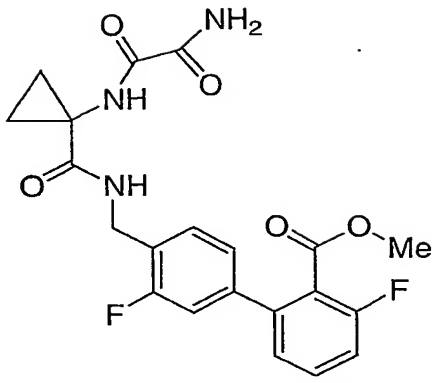
Methyl 3,3'-difluoro-4'-({[(1-{[methoxy(oxo)acetyl]amino}cyclopropyl)-carbonyl]amino}methyl)-1,1'-biphenyl-2-carboxylate



To a solution of methyl 4'-({[(1-aminocyclopropyl)carbonyl]amino}-methyl)-3,3'-difluoro-1,1'-biphenyl-2-carboxylate (0.25 g, 0.724 mmol, perpared according to the procedure described in Example 1) in methylene chloride 92 mL at 0 °C was added triethylamine (0.2mL 1.44mmol) followed by chloromethyl oxalate (0.07mL, 0.76 mmol). The reaction mixture was stirred at room temperature for 3 hours and then poured into water and extracted with methylene chloride. The organics were dried over sodium sulfate, filtered, and then concentrated to obtain the crude product. This crude product was passed through a silica pad, eluting with 3:1 methylene chloride:EtOAc to afford the title compound as a glass. Purity was determined by LCMS (ES MS, M^++H found:446) and proton NMR (400 MHz, $CDCl_3$: δ 7.71 (1H, s), 7.45(1H, dt, J=5.7 and 8.1Hz), 7.35 (1H, t, J=7.8Hz), 7.20-7.00 (4H, m), 6.79 (1H, m), 4.51(2H, d ,J=6.0Hz), 3.88(3H, s), 3.74(3H, s), 1.68(2H, m), 1.11 (2H, m) ppm.

EXAMPLE 6

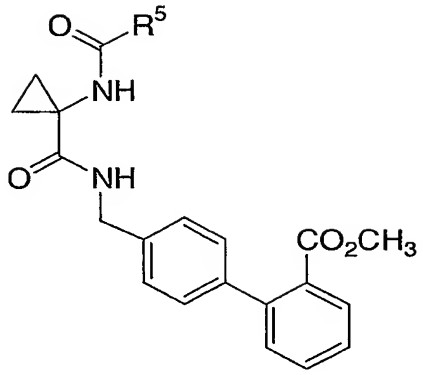
Methyl 4'-({[(1-{[amino(oxo)acetyl]amino}cyclopropyl)carbonyl]amino}methyl)-3,3'-difluoro-1,1'-biphenyl-2-carboxylate



To a solution of methyl 3,3'-difluoro-4'-({[(1-{[methoxy(oxo)acetyl]-amino}cyclopropyl)carbonyl]amino}methyl)-1,1'-biphenyl-2-carboxylate (0.02 g, 0.045 mmol, Example 5) in methylene chloride (2 mL) at room temperature was added ammonia (0.224mL of a 2M solution in methanol, 0.45mmol). The reaction mixture was stirred at room temperature for 4 hrs and then concentrated to obtain the crude product. This crude product was purified by reverse phase HPLC (Vydac column #218TP1022, gradient elution 5-95% acetonitrile :water containing 0.1% TFA). The pure fractions were lyophilized to afford the title compound as a solid. Purity was determined by LCMS (ES MS, M^++H found:432) and proton NMR (400 MHz, $CDCl_3$: δ 7.86 (1H,s), 7.45(1H,dt, J=5.7 and 8.1Hz), 7.35 (1H, t, J=7.8Hz), 7.20-7.00 (4H,m), 6.59 (1H, m), 5.61(1H, s), 4.54 (2H, d,J=6.0Hz), 3.74(3H,s), 1.68(2H,m), 1.12 (2H,m) ppm.

The following compounds in Table 1 were prepared by methods analogous to those described in Example 1.

Table 1



5

Example	R^5	ES MS, M+H+
7	isoxazol-5-yl	420
8	cyanomethyl	392
9	1-hydroxypropyl	411
10	1-cyanocyclopropyl	418
11	3,5-bis(trifluoromethyl)phenyl	565
12	2,4-difluorophenyl	465
13	2-propyl	395
14	4-methylphenyl	443
15	methoxymethyl	397
16	cyclopropyl	393
17	thien-2-ylmethyl	449
18	3,4-dimethoxybenzyl	503
19	pyridin-3-yl	430
20	pyridin-4-yl	430
21	1-benzothien-2-yl	485
22	3-methoxy-3-oxopropyl	439
23	3,4-dimethoxyphenyl	489
24	benzyl	443
25	isobutyl	409

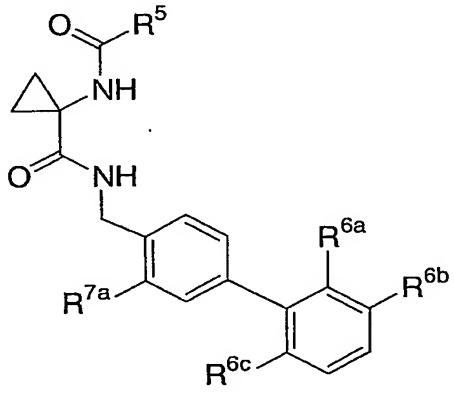
Example	R^5	ES MS, M+H+
26	2-phenylethyl	457
27	cyclopentyl	421
28	4-cyanophenyl	454
29	3-nitrophenyl	474
30	1-ethylpropyl	423
31	2-phenylcyclopropyl	469
32	2-naphthyl	479
33	2-furyl	419
34	thien-2-yl	435
35	1,3-benzodioxol-5-yl	473
36	(phenylthio)methyl	475
37	5-methylisoxazol-3-yl	434
38	phenoxymethyl	459
39	2,2-dimethylpropyl	423
40	2-cyclopentylethyl	449
41	2-methoxy-2-oxoethyl	425
42	(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-methyl	512
43	2-methoxyethyl	411
44	but-3-ynyl	405
45	ethoxymethyl	411
46	tetrahydrofuran-3-yl	423
47	2-nitroethyl	426
48	4-methyl-1,2,5-oxadiazol-3-yl	435
49	3-cyanophenyl	454
50	2-cyanophenyl	454
51	6-hydroxypyridin-2-yl	446
52	1-oxidopyridin-3-yl	446
53	6-choropyridin-2-yl	464
54	1-methyl-1H-pyrazol-4-yl	433
55	1H-pyrazol-1-ylmethyl	433

Example	R^5	ES MS, M+H+
56	1-methyl-1H-imidazol-2-yl	433
57	1H-1,2,4-triazol-1-ylmethyl	434
58	thiazol-4-yl	436
59	5-oxotetrahydrofuran-2-yl	437
60	2-oxo-2H-pyran-5-yl	447
61	6-methylpyridin-2-yl	444
62	6-oxo-1,6-dihydropyridazin-3-yl	447
63	3,5-dimethylisoxazol-4-yl	448
64	1H-pyrazol-5-yl	419
65	isoxazol-3-yl	420
66	oxazol-5-yl	420
67	pyridazin-3-yl	431
68	pyrimidin-5-yl	431
69	pyrimidin-4-yl	431
70	1H-imidazol-1-ylmethyl	433
71	1-methyl-1H-pyrazol-5-yl	433
72	1-methyl-1H-pyrazol-3-yl	433
73	thiazol-5-yl	436
74	(5-methyl-1H-pyrazol-1yl)methyl	447
75	(3-methyl-1H-1,2,4-triazol-5-yl)methyl	448
76	2-(1H-1,2,4-triazol-1-yl)ethyl	448
77	5-methyl-thiazol-4-yl	450
78	phenyl	429
79	3-fluorophenyl	447
80	3-methoxyphenyl	459
81	3-chlorophenyl	463
82	3,4-dichlorophenyl	497
83	3-(trifluoromethyl)phenyl	497
84	3-methylphenyl	443
85	quinoxalin-2-yl	481
86	3,5-dichlorophenyl	497

Example	R^5	ES MS, M+H+
87	2-chloropyridin-3-yl	464
88	3-hydroxyphenyl	445
89	3-nitro-5-(trifluoromethyl)phenyl	542
90	5-bromopyridin-3-yl	508
91	5-methyl-1-oxidopyridin-3-yl	459
92	5-hydroxypyridin-3-yl	446
93	5-bromo-1-oxidopyridin-3-yl	524
94	5-(methoxycarbonyl)pyridin-3-yl	488
95	tert-butyl	409
96	5-(carboxy)pyridin-3-yl	474
97	trifluoromethyl	421
98	3-(trifluoromethyl)pyridin-4-yl	498
99	5-(trifluoromethyl)pyridin-3-yl	498

The following compounds in Table 2 were prepared by methods analogous to those described in REFERENCE PROCEDURE 1.

Table 2



Ex.	R^5	R^{6a}	R^{6b}	R^{6c}	R^{7a}	ES MS, M+H+
100	2,2,2-trifluoroethyl	CO_2Me	F	H	F	471

Ex.	R^5	R^{6a}	R^{6b}	R^{6c}	R^{7a}	ES\MS, M+H+
101	Cyanomethyl	CO_2Me	F	H	F	428
102	Isoxazol-5-yl	CO_2Me	F	H	F	456
103	2,2,2-trifluoroethyl	trifluoromethyl	F	H	F	481
104	Isoxazol-5-yl	trifluoromethyl	F	H	F	466
105	2,2,2-trifluoroethyl	(methylamino)sulfonyl	H	H	F	488
106	Isoxazol-5-yl	(methylamino)sulfonyl	H	H	F	473
107	Pyrimidin-5-yl	CO_2Me	F	H	F	467
108	Isoxazol-5-yl	CO_2Me	Cl	H	F	472
109	2,2,2-trifluoroethyl	CO_2Me	Cl	H	F	487
110	Isoxazol-5-yl	CO_2Me	F	F	H	456
111	2,2,2-trifluoroethyl	CO_2Me	F	F	H	471
112	2,2,2-trifluoroethyl	CO_2Me	F	Me	H	467
113	2,2,2-trifluoroethyl	CO_2Me	Cl	Me	H	483
114	Isoxazol-5-yl	CO_2Me	F	Me	H	452
115	Isoxazol-5-yl	CO_2Me	Cl	Me	H	468
116	2,2,2-trifluoroethyl	CO_2Me	F	H	Cl	487
117	Pyrimidin-5-yl	CO_2Me	F	H	Cl	483
118	2,2,2-trifluoroethyl	CO_2Me	F	H	H	453
119	Pyrimidin-5-yl	CO_2Me	F	H	H	449
120	Isoxazol-5-yl	CO_2Me	F	H	Cl	472
121	Isoxazol-5-yl	2-CH_3-2H-tetrazol-5-yl	F	H	F	480
122	2,2,2-trifluoroethyl	2-CH_3-2H-tetrazol-5-yl	F	H	F	495
123	Pyrimidin-5-yl	2-CH_3-2H-tetrazol-5-yl	F	H	F	491
124	Pyrimidin-5-yl	trifluoromethyl	F	H	F	477
125	isoxazol-5-yl	3-CH_3-1,2,4-oxadiazol-5-yl	F	H	F	480
126	2,2,2-trifluoroethyl	3-CH_3-1,2,4-oxadiazol-5-yl	F	H	F	495
127	pyrimidin-5-yl	3-CH_3-1,2,4-oxadiazol-5-yl	F	H	F	491
128	2,2,2-trifluoroethyl	methoxy	F	H	F	443
129	pyrimidin-5-yl	methoxy	F	H	F	439
130	isoxazol-5-yl	methoxy	F	H	F	428
131	cyclopropyl	CO_2Me	F	H	Cl	445

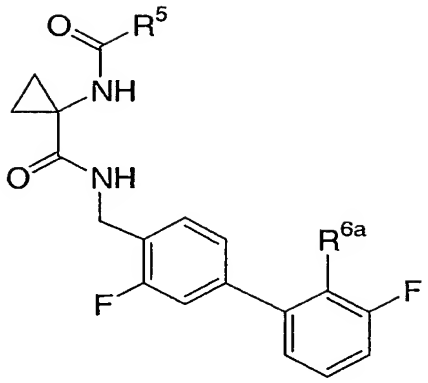
Ex.	R^5	R^{6a}	R^{6b}	R^{6c}	R^{7a}	ES MS, M+H+
132	cyclopropyl	CO_2Me	F	H	H	411
133	pyrimidin-5-yl	(methylamino)carbonyl	Cl	H	F	482
134	pyrimidin-5-yl	Cl	Cl	H	F	459
135	pyrimidin-5-yl	CO_2Me	F	H	OCH_3	479
136	trifluoromethyl	CO_2Me	F	H	F	457
137	dichloromethyl	CO_2Me	F	H	F	471
138	ethenyl	CO_2Me	F	H	F	415
139	(1E)-propenyl	CO_2Me	F	H	F	429
140	propyl	CO_2Me	F	H	F	431
141	difluoromethyl	CO_2Me	F	H	F	439
142	methyl	CO_2Me	F	H	F	403
143	pyrimidin-5-yl	1-methyl-ethyl	H	H	F	433
144	pyrimidin-5-yl	CO_2Me	F	H	OH	465
145	pyrimidin-5-yl	CO_2H	F	H	OH	451
146	pyrimidin-5-yl	H	H	H	H	373
147	pyrimidin-5-yl	CO_2Me	F	H	$NHCH_3$	478
148	fur-3-yl	CO_2Me	F	H	H	437
149	(methylsulfonyl)-methyl	CO_2Me	F	H	H	463
150	trifluoromethyl	trifluoromethyl	F	H	F	467
151	1,1-dichloroethyl	CO_2Me	F	H	F	485
152	trifluoromethyl	2-CH_3-2H-tetrazol-5-yl	F	H	F	481
153	trifluoromethyl	methoxy	F	H	F	429
154	dichloromethyl	2-CH_3-2H-tetrazol-5-yl	F	H	F	495
155	5-(trifluoromethyl)-pyridin-3-yl	CO_2Me	F	H	F	534
156	trifluoromethyl	3-CH_3-1,2,4-oxadiazol-5-yl	F	H	F	481
157	1,1-dichloroethyl	3-CH_3-1,2,4-oxadiazol-5-yl	F	H	F	509
158	2-carboxyethyl	CO_2Me	F	H	F	461
159	chlorodifluoro-methyl	CO_2Me	F	H	F	473

Ex.	R5	R6a	R6b	R6c	R7a	ES MS, M+H+
160	[(t-butoxycarbonyl)-amino]methyl	CO_2Me	F	H	F	518
161	aminomethyl	CO_2Me	F	H	F	418
162	5-bromopyridin-3-yl	CO_2Me	F	H	F	544
163	pyrimidin-5-yl	CO_2Me	Cl	H	F	483
164	acetylaminomethyl	CO_2Me	F	H	F	460
165	hydroxymethyl	CO_2Me	F	H	F	419
166	2-oxo-2-(pyridin-3-yl)ethyl	CO_2Me	F	H	F	508
167	trifluoromethyl	CO_2Me	Cl	H	F	473
168	phenyl	CO_2Me	F	H	F	465
169	bromomethyl	CO_2Me	F	H	F	481
170	trifluoromethyl	CO_2Me	H	F	F	457
171	pyrimidin-5-yl	CO_2Me	H	F	F	467
172	1-[(t-butoxy-carbonyl)amino]-ethyl	CO_2Me	F	H	F	532
173	(1R)-1-aminoethyl	CO_2Me	F	H	F	432
174	(1R)-1-(acetyl-amino)ethyl	CO_2Me	F	H	F	474
175	5-bromo-1-oxido-pyridin-3-yl	CO_2Me	F	H	F	560
176	trifluoromethyl	CO_2Me	CH_3	H	F	453
177	pyrimidin-5-yl	CO_2Me	CH_3	H	F	463
178	pyrimidin-5-yl	CO_2Me	F	H	SO_2CH_3	527
179	pyrimidin-5-yl	Br	H	H	F	469
180	pyrimidin-5-yl	(methoxycarbonyl)amino	F	H	F	482
181	pyrimidin-5-yl	(ethoxycarbonyl)amino	F	H	F	496
182	pyrimidin-5-yl	(2-fluoroethoxycarbonyl)-amino	F	H	F	514
183	trifluoromethyl	(methoxycarbonyl)amino	F	H	F	472
184	1,1-difluoro-3-	CO_2Me	F	H	F	483

Ex.	R^5	R^{6a}	R^{6b}	R^{6c}	R^{7a}	ES MS, M+H+
	hydroxypropyl					
185	dimethylamino-methyl	CO_2Me	F	H	F	446
186	5-chloropyridin-3-yl	CO_2Me	F	H	F	500
187	5-fluoropyridin-3-yl	CO_2Me	F	H	F	484
188	pyrimidin-5-yl	dimethylamino	H	H	F	434
189	2-hydroxypyridin-3-yl	CO_2Me	F	H	F	482
190	2-methoxypyridin-3-yl	CO_2Me	F	H	F	496
191	2-hydroxyphenyl	CO_2Me	F	H	F	481
192	trifluoromethyl	[(methoxycarbonyl)amino] methyl	F	H	F	486
193	pyrimidin-5-yl	[(methoxycarbonyl)amino] methyl	F	H	F	496
194	trifluoromethyl	{[(methoxycarbonyl)amino] carbonyl}amino	F	H	F	515
195	pyrimidin-5-yl	{[(methoxycarbonyl)amino] carbonyl}amino	F	H	F	525
196	2-oxopropyl	CO_2Me	F	H	F	445
197	2-methoxy-2-oxo-ethyl	CO_2Me	F	H	F	461
198	pentafluoroethyl	CO_2Me	F	H	F	507
199	trifluoromethyl	(methylamino)carbonyl	Cl	H	Cl	488
200	1-hydroxyethyl	CO_2Me	F	H	F	433
201	trifluoromethyl	(methylamino)carbonyl	F	H	F	456
202	2-hydroxypropyl	CO_2Me	F	H	F	447
203	1-(1-hydroxyethyl)-vinyl	CO_2Me	F	H	F	459

The following compounds in Table 3 were prepared by methods analogous to those described in REFERENCE PROCEDURE 2.

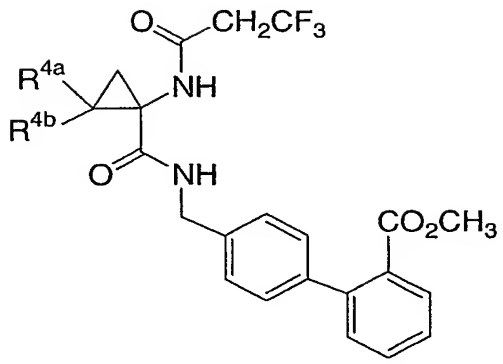
Table 3



Example	R^5	R^{6a}	ES MS, M+H+
204	isoxazol-5-yl	(methoxyamino)carbonyl	471
205	isoxazol-5-yl	(dimethylamino)carbonyl	469
206	2,2,2-trifluoroethyl	(dimethylamino)carbonyl	484
207	isoxazol-5-yl	(methylamino)carbonyl	455
208	2,2,2-trifluoroethyl	(methylamino)carbonyl	470
209	2,2,2-trifluoroethyl	(methoxyamino)carbonyl	486
210	pyrimidin-5-yl	(cyclobutyloxy)carbonyl	507
211	pyrimidin-5-yl	(isopropylamino)carbonyl	494
212	pyrimidin-5-yl	(ethylamino)carbonyl	480
213	pyrimidin-5-yl	(isopropyloxy)carbonyl	495

The following compounds in Table 4 were prepared by elaboration of the compound of Example 3 using procedures well known to those skilled in the art.

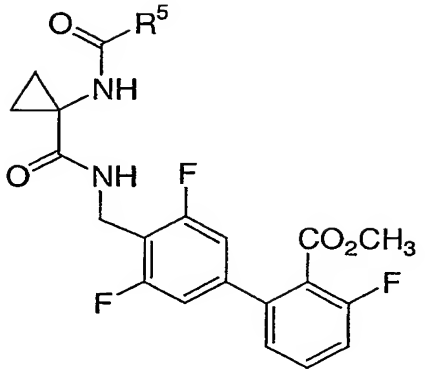
Table 4



Example	R^{4a}/R^{4b}	Stereochemistry	ES MS, M+H+	Starting material	Reagent
214	hydroxymethyl, H	(±)-*cis*	465	3	K_2CO_3 /MeOH
215	chloromethyl, H	(±)-*cis*	483	217	$SOCl_2$
216	CH_2	(±)	447	217	$SOCl_2$
217	[(methylsulfonyl)oxy]methyl, H	(±)-*cis*	543	217	MsCl
218	(methylthio)methyl, H	(±)-*cis*	495	220	NaSMe
219	(dimethylamino)methyl, H	(±)-*cis*	492	220	Me_2NH

The following compounds in Table 5 were prepared by methods analogous to those described in REFERENCE PROCEDURE 1.

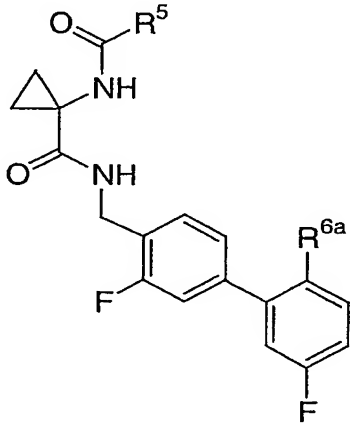
Table 5



Example	R^5	ES MS, M+H+
220	pyrimidin-5-yl	485
221	trifluoromethyl	475

The following compounds in Table 6 were prepared by methods analogous to those described in REFERENCE PROCEDURE 1.

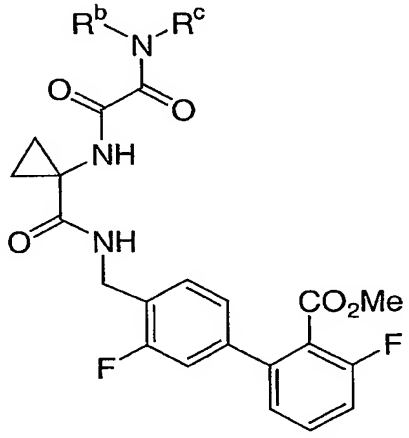
Table 6



Example	R^5	R^{6a}	R^{6b}	ES MS, M+H+
222	pyrimidin-5-yl	formyl	H	437
223	pyrimidin-5-yl	1-hydroxyethyl	H	453
224	trifluoromethyl	3-methyl-1,2,4-oxadiazol-5-yl	H	481
225	pyrimidin-5-yl	3-methyl-1,2,4-oxadiazol-5-yl	H	491
226	trifluoromethyl	CO_2Me	H	457

The following compounds in Table 7 were prepared by methods analogous to those described in Example 6.

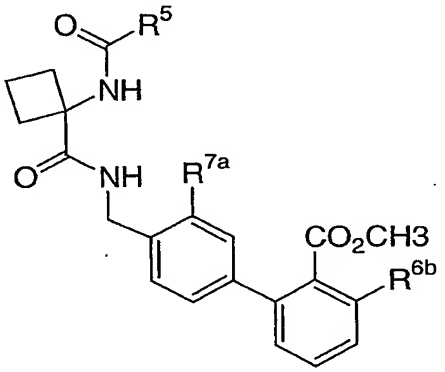
Table 7



Example	R^b	R^c	ES MS, M+H+
227	methyl	H	446
228	methyl	methyl	460
229	2-(dimethylamino)ethyl	H	503
230	2-(methylsulfonyl)ethyl	H	538
231	benzyl	H	522
232	2-phenylethyl	H	536

The following compounds in Table 8 were prepared by methods analogous to those described in Example 1, using the commercially available 1-[(tert-butoxycarbonyl)amino]cyclobutanecarboxylic acid instead of 1-[(tert-butoxy-carbonyl)amino]cyclopropanecarboxylic acid.

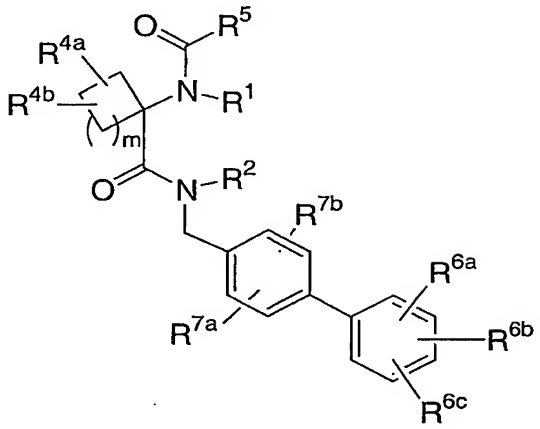
Table 8



Example	R5	R6b	R7a	ES MS, M+H+
233	pyrimidin-5-yl	H	H	445
234	pyrimidin-5-yl	H	F	463
235	pyrimidin-5-yl	F	F	481
236	CH_2CF_3	H	H	449

WHAT IS CLAIMED IS:

1. A compound of formula I



I

wherein

R^1 and R^2 are independently selected from

(1) hydrogen and

(2) C_{1-4} alkyl;

R^{4a} and R^{4b} are independently selected form

(1) hydrogen,

(2) halogen, and

(3) C_{1-4} alkyl optionally substituted with 1 to 4 groups selected from halogen, OR^a, $OC(O)R^a$, $S(O)_kR^d$, $OS(O)_2R^d$, and NR^1R^2, or

R^{4a} and R^{4b} together with the carbon atom to which they are both attached form an exo-cyclic methylene optionally substituted with 1 to 2 groups selected from C_{1-4} alkyl optionally substituted with 1-5 halogens and C_{1-4} alkyloxy;

R^5 is selected from

(1) C_{1-6} alkyl optionally substituted with 1 to 5 groups independently selected from halogen, nitro, cyano, OR^a, SR^a, COR^a, SO_2R^d, CO_2R^a, $OC(O)R^a$, NR^bR^c, $NR^bC(O)R^a$, $NR^bC(O)_2R^a$, $C(O)NR^bR^c$, C_{3-8} cycloalkyl,

(2) C_{3-8} cycloalkyl optionally substituted with 1 to 5 groups independently selected from halogen, nitro, cyano and phenyl,

(3) C_{3-6} alkynyl,

(4) C_{2-6} alkenyl optionally substituted with hydroxyethyl,

(5) $(CH_2)_k$-aryl optionally substituted with 1 to 3 groups independently selected from halogen, nitro, cyano, OR^a, SR^a, $C(O)_2R^a$, C_{1-4} alkyl and C_{1-3} haloalkyl, wherein aryl is selected from phenyl, 3,4-methylenedioxyphenyl and naphthyl;

(6) $(CH_2)_k$-heterocycle optionally substituted with 1 to 3 groups independently selected from halogen, nitro, cyano, OR^a, SR^a, C_{1-4} alkyl and C_{1-3} haloalkyl wherein said heterocycle is selected from (a) a 5-membered heteroaromatic ring having a ring heteroatom selected from N, O and S, and optionally having up to 3 additional ring nitrogen atoms wherein said ring is optionally benzo-fused; (b) a 6-membered heteroaromatic ring containing from 1 to 3 ring nitrogen atoms and N-oxides thereof, wherein said ring is optionally benzo-fused; and (c) a 5- or 6-membered non-aromatic heterocyclic ring selected from tetrahydrofuranyl, 5-oxo-tetrahydrofuranyl, 2-oxo-2H-pyranyl, 6-oxo-1,6-dihydropyridazinyl,

(7) $C(O)_2R^a$, and

(8) $C(O)NR^bR^c$;

R^{6a} is selected from

(1) C_{1-8} alkyl optionally substituted with 1-5 groups independently selected from halogen, nitro, cyano, COR^a, CO_2R^a, $C(O)NR^bR^c$, OR^a, $OC(O)R^a$, SR^a, SO_2R^d, $S(O)R^d$, NR^bR^c, $NR^bC(O)R^a$, $NR^bSO_2R^d$, $NR^bCO_2R^a$,

(2) C_{3-8} cycloalkyl,

(3) C_{2-8} alkenyl optionally substituted with CO_2R^a,

(4) halogen,

(5) cyano,

(6) nitro,

(7) NR^bR^c,

(8) $NR^bC(O)R^a$,

(9) $NR^bCO_2R^a$,

(10) $NR^bC(O)NR^bR^c$,

(11) $NR^bC(O)NR^bCO_2R^a$,

(12) $NR^bSO_2R^d$,

(13) CO_2R^a,

(14) COR^a,

(15) $C(O)NR^bR^c$,

(16) $C(O)NHOR^a$,

(17) $C(=NOR^a)R^a$,

(18) $C(=NOR^a)NR^bR^c$,

(19) OR^a,

(20) $OC(O)R^a$,

(21) $S(O)_kR^d$,

(22) $SO_2NR^bR^c$, and

(23) optionally substituted heterocycle where the heterocycle is a 5-membered heteroaromatic ring having a ring heteroatom selected from N, O and S, and optionally having up to 3 additional ring nitrogen atoms, 4,5-dihydro-oxazolyl and 4,5-dihydro-1,2,4-oxadiazolyl, and wherein said substituent is 1 to 3 groups independently selected from C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms, OR^a or $OC(O)R^a$,

R^{6b} and R^{6c} are independently selected from

(1) hydrogen, and

(2) a group from R^{6a}; with the proviso that not more than one of R^{6a}, R^{6b}, and R^{6c} is a heterocycle;

R^{7a} and R^{7b} are independently selected from

(1) hydrogen,

(2) halogen,

(3) cyano,

(4) nitro,

(5) OR^a,

(6) CO_2R^a,

(7) $C(O)NR^bR^c$,

(8) C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms,

(9) NR^bR^c, and

(10) $S(O)_kR^d$;

R^a is selected from

(1) hydrogen,

(2) C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms,

(3) phenyl optionally substituted with 1 to 3 groups independently selected from halogen, cyano, nitro, OH, C_{1-4} alkyloxy, C_{3-6} cycloalkyl and C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms,

(4) C_{3-6} cycloalkyl, and

(5) pyridyl optionally substituted with 1 to 3 groups independently selected from halogen and C_{1-4} alkyl;

R^b and R^c are independently selected from

(1) hydrogen,

(2) C_{1-4} alkyl optionally substituted with 1 to 5 groups independently selected from halogen , amino, mono-C_{1-4}alkylamino, di-C_{1-4}alkylamino, and SO_2R^d,

(3) $(CH_2)_k$-phenyl optionally substituted with 1 to 3 groups selected from halogen, cyano, nitro, OH, C_{1-4} alkyloxy, C_{3-6} cycloalkyl and C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms, and

(4) C_{3-6} cycloalkyl, or

R^b and R^c together with the nitrogen atom to which they are attached form a 4-, 5-, or 6-membered ring optionally containing an additional heteroatom selected from N, O, and S; or

R^b and R^c together with the nitrogen atom to which they are attached form a cyclic imide;

R^d is selected from

(1) C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms,

(2) C_{1-4} alkyloxy, and

(3) phenyl optionally substituted with 1 to 3 groups selected from halogen, cyano, nitro, OH, C_{1-4} alkyloxy, C_{3-6} cycloalkyl and C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms;

k is 0, 1 or 2; and

m is 0 or 1.

2. A compound of Claim 1 wherein R^1 and R^2 are each hydrogen.

3. A compound of Claim 1 wherein one of R^{4a} and R^{4b} is hydrogen and the other is selected from hydrogen, halogen and C_{1-4} alkyl optionally substituted with a group selected from halogen, OR^a, $OC(O)R^a$, $S(O)_kR^d$, $OS(O)_2R^d$ and NR^1R^2, or R^{4a} and R^{4b} together with the carbon atom to which they are both attached form an exo-cyclic methylene.

4. A compound of Claim 1 wherein R^{4a} and R^{4b} are each hydrogen.

5. A compound of Claim 1 wherein R^{4a} is hydrogen and R^{4b} is selected from CH_2-halogen, CH_2-OR^a, CH_2-$OC(O)R^a$, CH_2-$S(O)_kR^d$, CH_2-$OS(O)_2R^d$, and CH_2-NR^1R^2.

6. A compound of Claim 1 wherein R^5 is C_{1-6} alkyl optionally substituted with 1 to 5 groups independently selected from halogen, nitro, cyano, OR^a, SR^a, COR^a, SO_2R^d, CO_2R^a, $OC(O)R^a$, NR^bR^c, $NR^bC(O)R^a$, $C(O)NR^bR^c$, C_{3-8} cycloalkyl.

7. A compound of Claim 1 wherein R^5 is selected from C_{1-5} alkyl and C_{1-3} alkyl substituted with 1 to 3 groups selected from halogen, cyano, hydroxy, C_{1-4} alkoxy and C_{1-4} alkoxycarbonyl.

8. A compound of Claim 1 wherein R^5 is selected from C_{1-3} alkyl substituted with 1 to 3 groups selected from chloro, fluoro and cyano.

9. A compound of Claim 1 wherein R^5 is C_{3-6} cycloalkyl optionally substituted with 1 to 3 groups independently selected from halogen, nitro, cyano and phenyl.

10. A compound of Claim 1 wherein R^5 is $(CH_2)_k$-aryl optionally substituted with 1 to 3 groups independently selected from halogen, nitro, cyano, OR^a, SR^a, C_{1-4} alkyl and C_{1-3} haloalkyl, wherein aryl is selected from phenyl, 3,4-methylenedioxyphenyl and naphthyl.

11. A compound of Claim 1 wherein R^5 is phenyl optionally substituted with 1 to 2 groups selected from methyl, trifluoromethyl, halogen, cyano, nitro and methoxy.

12. A compound of Claim 1 wherein $(CH_2)_k$-heterocycle optionally substituted with 1 to 3 groups independently selected from halogen, nitro,

cyano, OR^a, SR^a, C_{1-4} alkyl and C_{1-3} haloalkyl wherein said heterocycle is selected from (a) a 5-membered heteroaromatic ring having a ring heteroatom selected from N, O and S, and optionally having up to 3 additional ring nitrogen atoms wherein said ring is optionally benzo-fused; and (b) a 6-membered heteroaromatic ring containing from 1 to 3 ring nitrogen atoms wherein said ring is optionally benzo-fused.

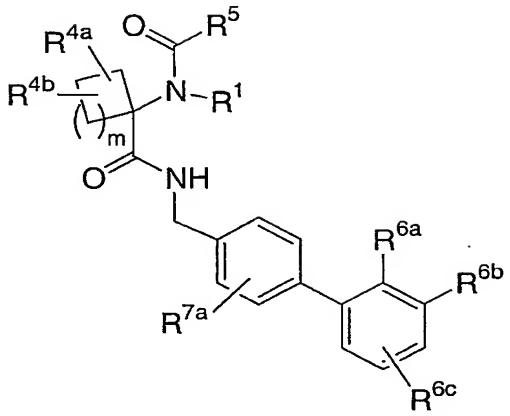
13. A compound of Claim 1 wherein R^5 is $(CH_2)_k$-heterocycle optionally substituted with 1 to 2 groups independently selected from halogen, nitro, cyano, OR^a, SR^a, C_{1-4} alkyl and C_{1-3} haloalkyl wherein said heterocycle is selected from isoxazolyl, thienyl, pyridinyl, benzothienyl, furyl, oxadiazolyl, 1-oxidopyridinyl, pyrazolyl, imidazolyl, 1,2,4-triazolyl, thiazolyl, 5-oxotetrahydrofuranyl, 2-oxo-2H-pyranyl, 6-oxo-1,6-dihydropyridazinyl, oxazolyl, pyridazinyl, pyrimidinyl and quinoxalinyl.

14. A compound of Claim 1 wherein R^5 is selected from isoxazolyl optionally substituted with 1 or 2 C_{1-4} alkyl, thienyl, pyridinyl optionally substituted with hydroxy or halogen, benzothienyl, furyl, tetrahydrofuranyl, oxadiazolyl optionally substituted with C_{1-4} alkyl, 1-oxidopyridinyl optionally substituted with C_{1-4} alkyl, pyrazolyl optionally substituted with C_{1-4} alkyl, imidazolyl optionally substituted with C_{1-4} alkyl, 1,2,4-triazolyl optionally substituted with C_{1-4} alkyl, thiazolyl optionally substituted with C_{1-4} alkyl, 5-oxotetrahydrofuranyl, 2-oxo-2H-pyranyl, 6-oxo-1,6-dihydropyridazinyl, oxazolyl, pyridazinyl, pyrimidinyl and quinoxalinyl.

15. A compound of Claim 1 wherein R^5 is selected from isoxazolyl optionally substituted with C_{1-4} alkyl, pyrimidinyl, pyridinyl optionally substituted with halogen or C_{1-4} alkyl and N-oxides thereof.

16. A compound of Claim 1 wherein R^5 is selected from C_{1-3} alkyl substituted with 1 to 3 halogen atoms, 5-isoxazole and 5-pyrimidinyl.

17. A compound of Claim 1 having the formula I(1):



I(1)

wherein m, R^1, R^{4a}, R^{4b}, R^5, R^{6a}, R^{6b}, R^{6c} and R^{7a} are as defined in Claim 1.

18. A compound of Claim 17 wherein R^{6a} is selected from (1) CO_2R^a, (2) $C(O)NHOR^a$, (3) cyano, (4) halogen, (5) OR^a, (6) C_{1-8} alkyl optionally substituted with 1-5 halogen atoms, or a group selected from CO_2R^a, $C(O)NR^bR^c$ and OR^a, (7) $C(O)NR^bR^c$, (8) $NR^bC(O)NR^bR^c$, (9) $NR^bC(O)OR^a$, and (10) optionally substituted heterocycle where the heterocycle is selected from oxadiazolyl and tetrazolyl and wherein said substituent is 1 to 3 groups independently selected from C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms, OR^a or $OC(O)R^a$.

19. A compound of Claim 17 wherein R^{6a} is selected from CO_2R^a, $C(O)NHOR^a$, methyltetrazolyl, methyloxadiazolyl, $NR^bC(O)NR^bR^c$, and $NR^bC(O)OR^a$.

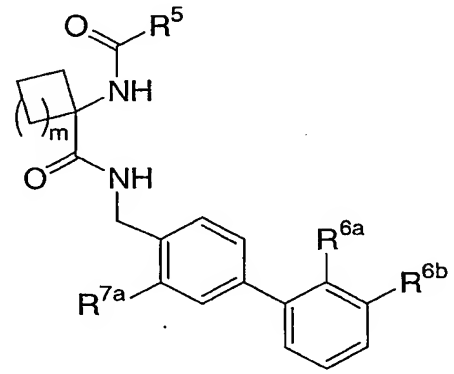
20. A compound of Claim 17 wherein R^{6b} is selected from hydrogen, halogen and CO_2R^a.

21. A compound of Claim 17 wherein R^{6b} is hydrogen, chloro or fluoro.

22. A compound of Claim 17 wherein R^5 is selected from C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms or a cyano group, C_{3-6}

cycloalkyl, isoxazolyl, pyrimidinyl and pyridinyl (and N-oxide thereof) optionally substituted with halogen.

23. A compound of Claim 1 having the formula I(2):



I(2)

wherein m, R^5, R^{6a}, R^{6b} and R^{7a} are as defined in Claim 1 .

24. A compound of Claim 23 wherein R^{6b} is hydrogen or halogen.

25. A compound of Claim 23 wherein R^{6b} is hydrogen.

26. A compound of Claim 23 wherein R^{6b} is fluorine or chlorine.

27. A compound of Claim 23 wherein R^{6a} is selected from (1) CO_2R^a, (2) $C(O)NHOR^a$, (3) cyano, (4) halogen, (5) OR^a, (6) C_{1-8} alkyl optionally substituted with 1-5 halogen atoms, or a group selected from CO_2R^a, $C(O)NR^bR^c$ and OR^a, (7) $C(O)NR^bR^c$, (8) $NR^bC(O)NR^bR^c$, (9) $NR^bC(O)OR^a$, and (10) optionally substituted heterocycle where the heterocycle is selected from oxadiazolyl and tetrazolyl and wherein said substituent is 1 to 3 groups independently selected from C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms, OR^a or $OC(O)R^a$.

28. A compound of Claim 23 wherein R^{6a} is selected from CO_2R^a, $C(O)NHOR^a$, methyltetrazolyl, methyloxadiazolyl, $NR^bC(O)NR^bR^c$, and $NR^bC(O)OR^a$.

29. A compound of Claim 23 wherein R^{6a} is selected from CO_2R^a, methyltetrazolyl and methyloxadiazolyl.

30. A compound of Claim 23 wherein In another embodiment R^{7a} is hydrogen or halogen.

31. A compound of Claim 23 wherein R^{7a} is hydrogen.

32. A compound of Claim 23 wherein R^{7a} is fluorine.

33. A compound of Claim 23 wherein R^5 is selected from C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms or a cyano group, C_{3-6} cycloalkyl, isoxazolyl, pyrimidinyl and pyridinyl (and N-oxide thereof) optionally substituted with halogen.

34. A compound of Claim 23 wherein m is 0 or 1, R^{6a} is 2-methyl-2H-tetrazol-5-yl, 3-methyl-1,2,4-oxadiazol-5-yl, CO_2R^a or $C(O)NHOR^a$ wherein R^a is C_{1-4} alkyl; R^{6b} is hydrogen, fluorine or chlorine; R^5 is selected from C_{1-4} alkyl optionally substituted with 1 to 5 halogen atoms or a cyano group, C_{3-6} cycloalkyl, isoxazolyl, pyrimidinyl and pyridinyl (and N-oxide thereof) optionally substituted with halogen or trifluoromethyl; and R^{7a} is hydrogen or fluorine.

35. A pharmaceutical composition comprising a therapeutically effective amount of a compuond of Claim 1 and pharmaceutically acceptable excipients.

36. A method of treatment or prevention of pain and inflammation comprising a step of administering, to a subject in need of such treatment or prevention, an effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

37. A method of treatment of osteoarthritis, repetitive motion pain, dental pain, cancer pain, myofascial pain, muscular injury pain, fibromyalgia pain, perioperative pain comprising a step of administering, to a subject in need of such

treatment, an effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

38. A method of treatment or prevention of inflammatory pain caused by chronic obstructive pulmonary disease, asthma, inflammatory bowel disease, rhinitis, pancreatitis, cystitis (interstitial cystitis), uveitis, inflammatory skin disorders, rheumatoid arthritis, edema resulting from trauma associated with burns, sprains or fracture, postsurgical intervention, osteoarthritis, rheumatic disease, teno-synovitis, or gout comprising a step of administering, to a subject in need of such treatment or prevention, an effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

39. A method of treatment or prevention of pain associated with angina, menstruation or cancer comprising a step of administering, to a subject in need of such treatment or prevention, an effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

40. A method of treatment of diabetic vasculopathy, post capillary resistance, diabetic symptoms associated with insulitis, psoriasis, eczema, spasms of the gastrointestinal tract or uterus, Crohn's disease, ulcerative colitis, or pancreatitis comprising a step of administering, to a subject in need of such treatment, an effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

41. A method of treatment or prevention of pain caused by pneumoconiosis, including aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis, byssinosis, adult respiratory distress syndrome, bronchitis, allergic rhinitis, vasomotor rhinitis, liver disease, multiple sclerosis, atherosclerosis, Alzheimer's disease, septic shock, cerebral edema, headache, migraine, closed head trauma, irritable bowel syndrome, or nephritis comprising a step of administering, to a subject in need of such treatment or prevention of pain, an effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

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(54) Title: N-BIPHENYLMETHYL AMINOCYCLOALKANECARBOXAMIDE DERIVATIVES

(57) Abstract: N-Biphenyl(substituted methyl) aminocycloalkanecarboxamide derivatives are bradykinin B1 antagonists or inverse agonists useful in the treatment or prevention of symptoms such as pain and inflammation associated with the bradykinin B1 pathway.

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A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CA 2,050,769 A (FRANZ et al) 11 March 1992, page 16, formula (IIe), page 1, line 1 and line 11 below the formula.	1-35

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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